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(54) G-CSF analog compositions and methods

G-CSF Analoge und Verfahren zu ihrer Herstellung

Analogues de G-CSF et méthodes pour les obtenir

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Description

Field of the Invention

5 [0001] This invention relates to granulocyte colony stimulating factor ("G-CSF") analogs.

Background

10 [0002] Hematopoiesis is controlled by two systems: the cells within the bone marrow microenvironment and growth factors. The growth factors, also called colony stimulating factors, stimulate committed progenitor cells to proliferate and to form colonies of differentiating blood cells. One of these factors is granulocyte colony stimulating factor, herein called G-CSF, which preferentially stimulates the growth and development of neutrophils, indicating a potential use in neutropenic states. Welte et al., PNAS-USA 82: 1526-1530 (1985); Souza et al., Science 232: 61-65 (1986) and Gabrilove, J. Seminars in Hematology 26: (2) 1-14 (1989).

15 [0003] In humans, endogenous G-CSF is detectable in blood plasma. Jones et al., Bailliere's Clinical Hematology 2 (1): 83-111 (1989). G-CSF is produced by fibroblasts, macrophages, T cells trophoblasts, expression product of a single copy gene comprised of four exons and five introns located on chromosome seventeen. Transcription of this locus produces a mRNA species which is differentially processed, resulting in two forms of G-CSF mRNA, one version coding for a protein of 177 amino acids, the other coding for a protein of 174 amino acids, Nagata et al., EMBO J 5: 575-581 (1986), and the form comprised of 174 amino acids has been found to have the greatest specific *in vivo* biological activity. G-CSF is species cross-reactive, such that when human G-CSF is administered to another mammal such as a mouse, canine or monkey, sustained neutrophil leukocytosis is elicited. Moore et al., PNAS-USA 84: 7134-7138 (1987).

20 [0004] Human G-CSF can be obtained and purified from a number of sources. Natural human G-CSF (nhG-CSF) can be isolated from the supernatants of cultured human tumor cell lines. The development of recombinant DNA technology, see, for instance, U.S. Patent 4,810,643 (Souza) incorporated herein by reference, has enabled the production of commercial scale quantities of G-CSF in glycosylated form as a product of eukaryotic host cell expression, and of G-CSF in non-glycosylated form as a product of prokaryotic host cell expression.

25 [0005] G-CSF has been found to be useful in the treatment of indications where an increase in neutrophils will provide benefits. For example, for cancer patients, G-CSF is beneficial as a means of selectively stimulating neutrophil production to compensate for hematopoietic deficits resulting from chemotherapy or radiation therapy. Other indications include treatment of various infectious diseases and related conditions, such as sepsis, which is typically caused by a metabolite of bacteria. G-CSF is also useful alone, or in combination with other compounds, such as other cytokines, for growth or expansion of cells in culture, for example, for bone marrow transplants.

30 [0006] Signal transduction, the way in which G-CSF effects cellular metabolism, is not currently thoroughly understood. G-CSF binds to a cell-surface receptor which apparently initiates the changes within particular progenitor cells, leading to cell differentiation.

35 [0007] Various altered G-CSF's have been reported. Generally, for design of drugs, certain changes are known to have certain structural effects. For example, deleting one cysteine could result in the unfolding of a molecule which is, in its unaltered state, is normally folded via a disulfide bridge. There are other known methods for adding, deleting or substituting amino acids in order to change the function of a protein.

40 [0008] Recombinant human G-CSF mutants have been prepared, but the method of preparation does not include overall structure/function relationship information. For example, the mutation and biochemical modification of Cys 18 has been reported. Kuga et al., Biochem. Biophys. Res. Comm 159: 103-111 (1989); Lu et al., Arch. Biochem. Biophys. 268: 81-92 (1989).

45 [0009] In U.S. Patent No. 4, 810, 643, entitled, "Production of Pluripotent Granulocyte Colony-Stimulating Factor" (as cited above), polypeptide analogs and peptide fragments of G-CSF are disclosed generally. Specific G-CSF analogs disclosed include those with the cysteins at positions 17, 36, 42, 64, and 74 (of the 174 amino acid species or of those having 175 amino acids, the additional amino acid being an N-terminal methionine) substituted with another amino acid, (such as serine), and G-CSF with an alanine in the first (N-terminal) position.

50 [0010] EP 0 335 423 entitled "Modified human G-CSF" reportedly discloses the modification of at least one amino group in a polypeptide having hG-CSF activity.

[0011] EP 0 272 703 entitled "Novel Polypeptide" reportedly discloses G-CSF derivatives having an amino acid substituted or deleted at or "in the neighborhood" of the N terminus.

55 [0012] EP 0 459 630, entitled "Polypeptides" reportedly discloses derivatives of naturally occurring G-CSF having at least one of the biological properties of naturally occurring G-CSF and a solution stability of at least 35% at 5 mg/ml in which the derivative has at least Cys¹⁷ of the native sequence replaced by a Ser¹⁷ residue and Asp²⁷ of the native sequence replaced by a Ser²⁷ residue.

[0013] EP 0 256 843 entitled "Expression of G-CSF and Muteins Thereof and Their Uses" reportedly discloses a

modified DNA sequence encoding G-CSF wherein the N-terminus is modified for enhanced expression of protein in recombinant host cells, without changing the amino acid sequence of the protein.

[0014] EP 0 243 153 entitled "Human G-CSF Protein Expression" reportedly discloses G-CSF to be modified by inactivating at least one yeast KEX2 protease processing site for increased yield in recombinant production using yeast.

[0015] Shaw, U.S. Patent No. 4,904,584, entitled "Site-Specific Homogeneous Modification of Polypeptides," reportedly discloses lysine altered proteins.

[0016] WO/9012874 reportedly discloses cysteine altered variants of proteins.

[0017] Australian patent application Document No. AU-A-10948/92, entitled, "Improved Activation of Recombinant Proteins" reportedly discloses the addition of amino acids to either terminus of a G-CSF molecule for the purpose of aiding in the folding of the molecule after prokaryotic expression.

[0018] Australian patent application Document No. AU-A-76380/91, entitled, "Muteins of the Granulocyte Colony Stimulating Factor (G-CSF)" reportedly discloses muteins of the granulocyte stimulating factor G-CSF in the sequence Leu-Gly-His-Ser-Leu-Gly-Ile at position 50-56 of G-CSF with 174 amino acids, and position 53 to 59 of the G-CSF with 177 amino acids, or/and at least one of the four histidine residues at positions 43, 79, 156 and 170 of the mature G-CSF with 174 amino acids or at positions 46, 82, 159, or 173 of the mature G-CSF with 177 amino acids.

[0019] GB 2 213 821, entitled "Synthetic Human Granulocyte Colony Stimulating Factor Gene" reportedly discloses a synthetic G-CSF-encoding nucleic acid sequence incorporating restriction sites to facilitate the cassette mutagenesis of selected regions, and flanking restriction sites to facilitate the incorporation of the gene into a desired expression system.

[0020] G-CSF has reportedly been crystallized to some extent, e.g., EP 344 796, and the overall structure of G-CSF has been surmised, but only on a gross level. Bazan, Immunology Today 11: 350-354 (1990); Parry et al., J. Molecular Recognition 8: 107-110 (1988). To date, there have been no reports of the overall structure of G-CSF, and no systematic studies of the relationship of the overall structure and function of the molecule, studies which are essential to the systematic design of G-CSF analogs. Accordingly, there exists a need for a method of this systematic design of G-CSF analogs, and the resultant compositions.

Summary of the Invention

[0021] The three dimensional structure of G-CSF has now been determined to the atomic level. From this three-dimensional structure, one can now forecast with substantial certainty how changes in the composition of a G-CSF molecule may result in structural changes. These structural characteristics may be correlated with biological activity to design and produce G-CSF analogs.

[0022] Although others had speculated regarding the three dimensional structure of G-CSF, Bazan, Immunology Today 11: 350-354 (1990); Parry et al., J. Molecular Recognition 8: 107-110 (1988), these speculations were of no help to those wishing to prepare G-CSF analogs either because the surmised structure was incorrect (Parry et al., *supra*) and/or because the surmised structure provided no detail correlating the constituent moieties with structure. The present determination of the three-dimensional structure to the atomic level is by far the most complete analysis to date, and provides important information to those wishing to design and prepare G-CSF analogs. For example, from the present three dimensional structural analysis, precise areas of hydrophobicity and hydrophilicity have been determined.

[0023] Relative hydrophobicity is important because it directly relates to the stability of the molecule. Generally, biological molecules, found in aqueous environments, are externally hydrophilic and internally hydrophobic; in accordance with the second law of thermodynamics provides, this is the lowest energy state and provides for stability. Although one could have speculated that G-CSF's internal core would be hydrophobic, and the outer areas would be hydrophilic, one would have had no way of knowing specific hydrophobic or hydrophilic areas. With the presently provided knowledge of areas of hydrophobicity/hilicity, one may forecast with substantial certainty which changes to the G-CSF molecule will affect the overall structure of the molecule.

[0024] As a general rule, one may use knowledge of the geography of the hydrophobic and hydrophilic regions to design analogs in which the overall G-CSF structure is not changed, but change does affect biological activity ("biological activity" being used here in its broadest sense to denote function). One may correlate biological activity to structure. If the structure is not changed, and the mutation has no effect on biological activity, then the mutation has no biological function. If, however, the structure is not changed and the mutation does affect biological activity, then the residue (or atom) is essential to at least one biological function. Some of the present working examples were designed to provide no change in overall structure, yet have a change in biological function.

[0025] Based on the correlation of structure to biological activity, the present invention relates to G-CSF analogs. These analogs are molecules which have more, fewer, different or modified amino acid residues from the G-CSF amino acid sequence. The modifications may be by addition, substitution, or deletion of one or more amino acid residues. The modification may include the addition or substitution of analogs of the amino acids themselves, such as peptidomimetics or amino acids with altered moieties such as altered side groups. The G-CSF used as a basis for comparison may

be of human, animal or recombinant nucleic acid-technology origin (although the working examples disclosed herein are based on the recombinant production of the 174 amino acid species of human G-CSF, having an extra N-terminus methionyl residue). The analogs may possess functions different from natural human G-CSF molecule, or may exhibit the same functions, or varying degrees of the same functions. For example, the analogs may be designed to have a higher or lower biological activity, have a longer shelf-life or a decrease in stability, be easier to formulate, or more difficult to combine with other ingredients. The analogs may have no hematopoietic activity, and may therefore be useful as an antagonist against G-CSF effect (as, for example, in the overproduction of G-CSF). From time to time herein the present analogs are referred to as proteins or peptides for convenience, but contemplated herein are other types of molecules, such as peptidomimetics or chemically modified peptides.

[0026] In another aspect, the present disclosure relates to related compositions containing a G-CSF analog as an active ingredient. The term, "related composition," as used herein, is meant to denote a composition which may be obtained once the identity of the G-CSF analog is ascertained (such as a G-CSF analog labeled with a detectable label, related receptor or pharmaceutical composition). Also considered a related composition are chemically modified versions of the G-CSF analog, such as those having attached at least one polyethylene glycol molecule.

[0027] For example, one may prepare a G-CSF analog to which a detectable label is attached, such as a fluorescent, chemiluminescent or radioactive molecule.

[0028] Another example is a pharmaceutical composition which may be formulated by known techniques using known materials, see, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pennsylvania 18042) pages 1435-1712, which are herein incorporated by reference. Generally, the formulation will depend on a variety of factors such as administration, stability, production concerns and other factors. The G-CSF analog may be administered by injection or by pulmonary administration via inhalation. Enteric dosage forms may also be available for the present G-CSF analog compositions, and therefore oral administration may be effective. G-CSF analogs may be inserted into liposomes or other microcarriers for delivery, and may be formulated in gels or other compositions for sustained release. Although preferred compositions will vary depending on the use to which the composition will be put, generally, for G-CSF analogs having at least one of the biological activities of natural G-CSF, preferred pharmaceutical compositions are those prepared for subcutaneous injection or for pulmonary administration via inhalation, although the particular formulations for each type of administration will depend on the characteristics of the analog.

[0029] Another example of related composition is a receptor for the present analog. As used herein, the term "receptor" indicates a moiety which selectively binds to the present analog molecule. For example, antibodies, or fragments thereof, or "recombinant antibodies" (see Huse et al., Science 246:1275 (1989)) may be used as receptors. Selective binding does not mean only specific binding (although binding-specific receptors are encompassed herein), but rather that the binding is not a random event. Receptors may be on the cell surface or intra- or extra-cellular, and may act to effectuate, inhibit or localize the biological activity of the present analogs. Receptor binding may also be a triggering mechanism for a cascade of activity indirectly related to the analog itself. Also contemplated herein are nucleic acids, vectors containing such nucleic acids and host cells containing such nucleic acids which encode such receptors.

[0030] Another example of a related composition is a G-CSF analog with a chemical moiety attached. Generally, chemical modification may alter biological activity or antigenicity of a protein, or may alter other characteristics, and these factors will be taken into account by a skilled practitioner. As noted above, one example of such chemical moiety is polyethylene glycol. Modification may include the addition of one or more hydrophilic or hydrophobic polymer molecules, fatty acid molecules, or polysaccharide molecules. Examples of chemical modifiers include polyethylene glycol, alkylpolyethylene glycols, DI-poly(amino acids), polyvinylpyrrolidone, polyvinyl alcohol, pyran copolymer, acetic acid/acylation, propionic acid, palmitic acid, stearic acid, dextran, carboxymethyl cellulose, pullulan, or agarose. See, Francis, *Focus on Growth Factors* 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20 0LD, UK). Also, chemical modification may include an additional protein or portion thereof, use of a cytotoxic agent, or an antibody. The chemical modification may also include lecithin.

[0031] In another aspect, the present disclosure relates to nucleic acids encoding such analogs. The nucleic acids may be DNAs or RNAs or derivatives thereof, and will typically be cloned and expressed on a vector, such as a phage or plasmid containing appropriate regulatory sequences. The nucleic acids may be labeled (such as using a radioactive, chemiluminescent, or fluorescent label) for diagnostic or prognostic purposes, for example. The nucleic acid sequence may be optimized for expression, such as including codons preferred for bacterial expression. The nucleic acid and its complementary strand, and modifications thereof which do not prevent encoding of the desired analog are here contemplated.

[0032] In another aspect, the present disclosure relates to host cells containing the above nucleic acids encoding the present analogs. Host cells may be eukaryotic or prokaryotic, and expression systems may include extra steps relating to the attachment (or prevention) of sugar groups (glycosylation), proper folding of the molecule, the addition or deletion of leader sequences or other factors incident to recombinant expression.

[0033] In another aspect the present disclosure relates to antisense nucleic acids which act to prevent or modify the

type or amount of expression of such nucleic acid sequences. These may be prepared by known methods.

[0034] In another aspect of the present disclosure, the nucleic acids encoding a present analog may be used for gene therapy purposes, for example, by placing a vector containing the analog-encoding sequence into a recipient so the nucleic acid itself is expressed inside the recipient who is in need of the analog composition. The vector may first be placed in a carrier, such as a cell, and then the carrier placed into the recipient. Such expression may be localized or systemic. Other carriers include non-naturally occurring carriers, such as liposomes or other microcarriers or particles, which may act to mediate gene transfer into a recipient.

[0035] The present disclosure also provides for computer programs for the expression (such as visual display) of the G-CSF or analog three dimensional structure, and further, a computer program which expresses the identity of each constituent of a G-CSF molecule and the precise location within the overall structure of that constituent, down to the atomic level. Set forth below is one example of such program. There are many currently available computer programs for the expression of the three dimensional structure of a molecule. Generally, these programs provide for inputting of the coordinates for the three dimensional structure of a molecule (i.e., for example, a numerical assignment for each atom of a G-CSF molecule along an x, y, and z axis), means to express (such as visually display) such coordinates, means to alter such coordinates and means to express an image of a molecule having such altered coordinates. One may program crystallographic information, i.e., the coordinates of the location of the atoms of a G-CSF molecule in three dimension space, wherein such coordinates have been obtained from crystallographic analysis of said G-CSF molecule, into such programs to generate a computer program for the expression (such as visual display) of the G-CSF three dimensional structure. Also provided, therefore, is a computer program for the expression of G-CSF analog three dimensional structure. Preferred is the computer program Insight II, version 4, available from Biosym, San Diego, California, with the coordinates as set forth in FIGURE 5 input. Preferred expression means is on a Silicon Graphics 320 VGX computer, with Crystal Eyes glasses (also available from Silicon Graphics), which allows one to view the G-CSF molecule or its analog stereoscopically. Alternatively, the present G-CSF crystallographic coordinates and diffraction data are also deposited in the Protein Data Bank, Chemistry Department, Brookhaven National Laboratory, Upton, New York 119723, USA. One may use these data in preparing a different computer program for expression of the three dimensional structure of a G-CSF molecule or analog thereof. Therefore, another aspect of the present invention is a computer program for the expression of the three dimensional structure of a G-CSF molecule. Also provided is said computer program for visual display of the three dimensional structure of a G-CSF molecule; and further, said program having means for altering such visual display. Apparatus useful for expression of such computer program, particularly for the visual display of the computer image of said three dimensional structure of a G-CSF molecule or analog thereof is also therefore here provided, as well as means for preparing said computer program and apparatus.

[0036] The computer program is useful for preparation of G-CSF analogs because one may select specific sites on the G-CSF molecule for alteration and readily ascertain the effect the alteration will have on the overall structure of the G-CSF molecule. Selection of said site for alteration will depend on the desired biological characteristic of the G-CSF analog. If one were to randomly change said G-CSF molecule (r-met-hu-G-CSF) there would be 175²⁰ possible substitutions, and even more analogs having multiple changes, additions or deletions. By viewing the three dimensional structure wherein said structure is correlated with the composition of the molecule, the selection for sites of alteration is no longer a random event, but sites for alteration may be determined rationally.

[0037] As set forth above, identity of the three dimensional structure of G-CSF, including the placement of each constituent down to the atomic level has now yielded information regarding which moieties are necessary to maintain the overall structure of the G-CSF molecule. One may therefore select whether to maintain the overall structure of the G-CSF molecule when preparing a G-CSF analog of the present invention, or whether (and how) to change the overall structure of the G-CSF molecule when preparing a G-CSF analog of the present invention. Optionally, once one has prepared such analog, one may test such analog for a desired characteristic.

[0038] One may, for example, seek to maintain the overall structure possessed by a non-altered natural or recombinant G-CSF molecule. The overall structure is presented in Figures 2, 3, and 4, and is described in more detail below. Maintenance of the overall structure may ensure receptor binding, a necessary characteristic for an analog possessing the hematopoietic capabilities of natural G-CSF (if no receptor binding, signal transduction does not result from the presence of the analog). It is contemplated that one class of G-CSF analogs will possess the three dimensional core structure of a natural or recombinant (non-altered) G-CSF molecule, yet possess different characteristics, such as an increased ability to selectively stimulate neutrophils. Another class of G-CSF analogs are those with a different overall structure which diminishes the ability of a G-CSF analog molecule to bind to a G-CSF receptor, and possesses a diminished ability to selectively stimulate neutrophils as compared to non-altered natural or recombinant G-CSF.

[0039] For example, it is now known which moieties within the internal regions of the G-CSF molecule are hydrophobic, and, correspondingly, which moieties on the external portion of the G-CSF molecule are hydrophilic. Without knowledge of the overall three dimensional structure, preferably to the atomic level as provided herein, one could not forecast which alterations within this hydrophobic internal area would result in a change in the overall structural conformation of the molecule. An overall structural change could result in a functional change, such as lack of receptor bind-

ing, for example, and therefore, diminishment of biological activity as found in non-altered G-CSF. Another class of G-CSF analogs is therefore G-CSF analogs which possess the same hydrophobicity as (non-altered) natural or recombinant G-CSF. More particularly, another class of G-CSF analogs possesses the same hydrophobic moieties within the four helical bundle of its internal core as those hydrophobic moieties possessed by (non-altered) natural or recombinant G-CSF yet have a composition different from said non-altered natural or recombinant G-CSF.

[0040] Another example relates to external loops which are structures which connect the internal core (helices) of the G-CSF molecule. From the three dimensional structure -- including information regarding the spatial location of the amino acid residues -- one may forecast that certain changes in certain loops will not result in overall conformational changes. Therefore, another class of G-CSF analogs provided herein is that having an altered external loop but possessing the same overall structure as (non-altered) natural or recombinant G-CSF. More particularly, another class of G-CSF analogs provided herein are those having an altered external loop, said loop being selected from the loop present between helices A and B; between helices B and C; between helices C and D; between helices D and A, as those loops and helices are identified herein. More particularly, said loops, preferably the AB loop and/or the CD loop are altered to increase the half life of the molecule by stabilizing said loops. Such stabilization may be by connecting all or a portion of said loop(s) to a portion of an alpha helical bundle found in the core of a G-CSF (or analog) molecule. Such connection may be via beta sheet, salt bridge, disulfide bonds, hydrophobic interaction or other connecting means available to those skilled in the art, wherein such connecting means serves to stabilize said external loop or loops. For example, one may stabilize the AB or CD loops by connecting the AB loop to one of the helices within the internal region of the molecule.

[0041] The N-terminus also may be altered without change in the overall structure of a G-CSF molecule, because the N-terminus does not effect structural stability of the internal helices, and, although the external loops are preferred for modification, the same general statements apply to the N-terminus.

[0042] Additionally, such external loops may be the site(s) for chemical modification because in (non-altered) natural or recombinant G-CSF such loops are relatively flexible and tend not to interfere with receptor binding. Thus, there would be additional room for a chemical moiety to be directly attached (or indirectly attached via another chemical moiety which serves as a chemical connecting means). The chemical moiety may be selected from a variety of moieties available for modification of one or more function of a G-CSF molecule. For example, an external loop may provide sites for the addition of one or more polymer which serves to increase serum half-life, such as a polyethylene glycol molecule. Such polyethylene glycol molecule(s) may be added wherein said loop is altered to include additional lysines which have reactive side groups to which polyethylene glycol moieties are capable of attaching. Other classes of chemical moieties may also be attached to one or more external loops, including but not limited to other biologically active molecules, such as receptors, other therapeutic proteins (such as other hematopoietic factors which would engender a hybrid molecule), or cytotoxic agents (such as diphtheria toxin). This list is of course not complete; one skilled in the art possessed of the desired chemical moiety will have the means to effect attachment of said desired moiety to the desired external loop. Therefore, another class of the present G-CSF analogs includes those with at least one alteration in an external loop wherein said alteration provides for the addition of a chemical moiety such as at least one polyethylene glycol molecule.

[0043] Deletions, such as deletions of sites recognized by proteins for degradation of the molecule, may also be effectual in the external loops. This provides alternative means for increasing half-life of a molecule otherwise having the G-CSF receptor binding and signal transduction capabilities (i.e., the ability to selectively stimulate the maturation of neutrophils). Therefore, another class of the present G-CSF analogs includes those with at least one alteration in an external loop wherein said alteration decreases the turnover of said analog by proteases. Preferred loops for such alterations are the AB loop and the CD loop. One may prepare an abbreviated G-CSF molecule by deleting a portion of the amino acid residues found in the external loops (identified in more detail below), said abbreviated G-CSF molecule may have additional advantages in preparation or in biological function.

[0044] Another example relates to the relative charges between amino acid residues which are in proximity to each other. As noted above, the G-CSF molecule contains a relatively tightly packed four helical bundle. Some of the faces on the helices face other helices. At the point (such as a residue) where a helix faces another helix, the two amino acid moieties which face each other may have the same charge, and thus tend to repel each other, which lends instability to the overall molecule. This may be eliminated by changing the charge (to an opposite charge or a neutral charge) of one or both of the amino acid moieties so that there is no repelling. Therefore, another class of G-CSF analogs includes those G-CSF analogs having been altered to modify instability due to surface interactions, such as electron charge location.

[0045] The present invention relates to methods for designing G-CSF analogs and related compositions and the products of those methods. The end products of the methods may be the G-CSF analogs as defined above or related compositions. For instance, the examples disclosed herein demonstrate (a) the effects of changes in the constituents (i.e., chemical moieties) of the G-CSF molecule on the G-CSF structure and (b) the effects of changes in structure on biological function. Essentially, therefore, an aspect of the present invention is a method for preparing a G-CSF analog

comprising the steps of:

- (a) viewing at an amino acid or atomic level information conveying the three dimensional structure of a G-CSF molecule as set forth in Figure 5 wherein the chemical moieties, such as each amino acid residue or each atom of each amino acid residue, of the G-CSF molecule are correlated with said structure;
- (b) selecting from said information a site on a G-CSF molecule for alteration;
- (c) preparing a G-CSF analog molecule having such alteration; and
- (d) optionally, testing such G-CSF analog molecule for a desired characteristic.

[0046] One may use the here provided computer programs for a computer-based method for preparing a G-CSF analog. Another aspect of the present invention is therefore a method for preparing a G-CSF analog according to the method of the preceeding paragraph based on the use of a computer comprising the steps of:

- (a) providing computer expression of the three dimensional structure of a G-CSF molecule wherein the chemical moieties, such as each amino acid residue or each atom of each amino acid residue, of the G-CSF molecule are correlated with said structure;
- (b) selecting from said computer expression a site on a G-CSF molecule for alteration;
- (c) preparing a G-CSF molecule having such alteration; and
- (d) optionally, testing such G-CSF molecule for a desired characteristic.

[0047] More specifically, the present invention provides a method for preparing a G-CSF analog comprising the steps of:

- (a) viewing at the amino acid or atomic level the three dimensional structure of a G-CSF molecule as set forth in Figure 5 via a computer, said computer programmed (i) to express the coordinates of a G-CSF molecule in three dimensional space, and (ii) to allow for entry of information for alteration of said G-CSF expression and viewing thereof;
- (b) selecting a site on said visual image of said G-CSF molecule for alteration;
- (c) entering information for said alteration on said computer;
- (d) viewing a three dimensional structure of said altered G-CSF molecule via said computer;
- (e) optionally repeating steps (a)-(c);
- (f) preparing a G-CSF analog with said alteration; and
- (g) optionally testing said G-CSF analog for a desired characteristic.

[0048] In another aspect, the present disclosure relates to methods of using the present G-CSF analogs and related compositions and methods for the treatment or protection of mammals, either alone or in combination with other hematopoietic factors or drugs in the treatment of hematopoietic disorders. It is contemplated that one aspect of designing G-CSF analogs will be the goal of enhancing or modifying the characteristics non-modified G-CSF is known to have.

[0049] For example, the analogs may possess enhanced or modified activities, so, where G-CSF is useful in the treatment of (for example) neutropenia, the present compositions and methods may also be of such use.

[0050] Another example is the modification of G-CSF for the purpose of interacting more effectively when used in combination with other factors particularly in the treatment of hematopoietic disorders. One example of such combination use is to use an early-acting hematopoietic factor (i.e., a factor which acts earlier in the hematopoiesis cascade on relatively undifferentiated cells) and either simultaneously or in seriatim use of a later-acting hematopoietic factor, such as G-CSF or analog thereof (as G-CSF acts on the CFU-GM lineage in the selective stimulation of neutrophils). The methods and compositions may be useful in therapy involving such combinations or "cocktails" of hematopoietic factors.

[0051] The compositions and methods may also be useful in the treatment of leukopenia, myogenous leukemia, severe chronic neutropenia, aplastic anemia, glycogen storage disease, mucositis, and other bone marrow failure states. The compositions and methods may also be useful in the treatment of hematopoietic deficits arising from chemotherapy or from radiation therapy. The success of bone marrow transplantation, or the use of peripheral blood progenitor cells for transplantation, for example, may be enhanced by application of the present compositions (proteins or nucleic acids for gene therapy) and methods. The compositions and methods may also be useful in the treatment of infectious diseases, such in the context of wound healing, burn treatment, bacteremia, septicemia, fungal infections, endocarditis, osteomyelitis, infection related to abdominal trauma, infections not responding to antibiotics, pneumonia and the treatment of bacterial inflammation may also benefit from the application of the compositions and methods. In addition, the compositions and methods may be useful in the treatment of leukemia based upon a reported ability to differentiate leukemic cells. Welte et al., PNAS-USA 82: 1526-1530 (1985). Other applications include the treatment of individuals with tumors, using the compositions and methods, optionally in the presence of receptors (such as antibody-

ies) which bind to the tumor cells. For review articles on therapeutic applications, see Lieshke and Burgess, N.Engl.J.Med. 327: 28-34 and 99-106 (1992) both of which are herein incorporated by reference.

[0052] The compositions and methods may also be useful to act as intermediaries in the production of other moieties; for example, G-CSF has been reported to influence the production of other hematopoietic factors and this function (if ascertained) may be enhanced or modified via the present compositions and/or methods.

[0053] The compositions related to the present G-CSF analogs, such as receptors, may be useful to act as an antagonist which prevents the activity of G-CSF or an analog. One may obtain a composition with some or all of the activity of non-altered G-CSF or a G-CSF analog, and add one or more chemical moieties to alter one or more properties of such G-CSF or analog. With knowledge of the three dimensional conformation, one may forecast the best geographic location for such chemical modification to achieve the desired effect.

[0054] General objectives in chemical modification may include improved half-life (such as reduced renal, immunological or cellular clearance), altered bioactivity (such as altered enzymatic properties, dissociated bioactivities or activity in organic solvents), reduced toxicity (such as concealing toxic epitopes, compartmentalization, and selective biodistribution), altered immunoreactivity (reduced immunogenicity, reduced antigenicity or adjuvant action), or altered physical properties (such as increased solubility, improved thermal stability, improved mechanical stability, or conformational stabilization). See Francis, *Focus on Growth Factors* 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20 0LD, UK).

[0055] The examples below are illustrative of the present invention and are not intended as a limitation. It is understood that variations and modifications will occur to those skilled in the art, and it is intended that the appended claims cover all such equivalent variations which come within the scope of the invention as claimed.

Detailed Description of the Drawings

[0056]

FIGURE 1 is an illustration of the amino acid sequence of the 174 amino acid species of G-CSF with an additional N-terminal methionine (Seq. ID No.: 1) (Seq. ID No.: 2).

FIGURE 2 is an topology diagram of the crystalline structure of G-CSF, as well as hGH, pGH, GM-CSF, INF-B, IL-2, and IL-4. These illustrations are based on inspection of cited references. The length of secondary structural elements are drawn in proportion to the number of residues. A, B, C, and D helices are labeled according to the scheme used herein for G-CSF. For INF- β , the original labeling of helices is indicated in parentheses. FIGURE 3 is an "ribbon diagram" of the three dimensional structure of G-CSF. Helix A is amino acid residues 11-39 (numbered according to Figure 1, above), helix B is amino acid residues 72-91, helix C is amino acid residues 100-123, and helix D is amino acid residues 143-173. The relatively short 3^{10} helix is at amino acid residues 45-48, and the alpha helix is at amino acid residues 48-53. Residues 93-95 form almost one turn of a left handed helix.

FIGURE 4 is a "barrel diagram" of the three dimensional structure of G-CSF. Shown in various shades of gray are the overall cylinders and their orientations for the three dimensional structure of G-CSF. The numbers indicate amino acid residue position according to FIGURE 1 above.

FIGURE 5 is a list of the coordinates used to generate a computer-aided visual image of the three-dimensional structure of G-CSF. The coordinates are set forth below. The columns correspond to separate field:

- (i) Field 1 (from the left hand side) is the atom,
- (ii) Field 2 is the assigned atom number,
- (iii) Field 3 is the atom name (according to the periodic table standard nomenclature, with CB being carbon atom Beta, CG is Carbon atom Gamma, etc.);
- (iv) Field 4 is the residue type (according to three letter nomenclature for amino acids as found in, e.g., Stryer, Biochemistry, 3d Ed., W.H. Freeman and Company, N.Y. 1988, inside back cover);
- (v) Fields 5-7 are the x-axis, y-axis and z-axis positions of the atom;
- (vi) Field 8 (often a "1.00") designates occupancy at that position;
- (vii) Field 9 designates the B-factor;
- (viii) Field 10 designates the molecule designation. Three molecules (designated a, b, and c) of G-CSF crystallized together as a unit. The designation a, b, or c indicates which coordinates are from which molecule. The number after the letter (1, 2, or 3) indicates the assigned amino acid residue position, with molecule A having assigned positions 10-175, molecule B having assigned positions 210-375, and molecule C having assigned positions 410-575. These positions were so designated so that there would be no overlap among the three molecules which crystallized together. (The "W" designation indicates water).

FIGURE 6 is a schematic representation of the strategy involved in refining the crystallization matrix for parameters

involved in crystallization. The crystallization matrix corresponds to the final concentration of the components (salts, buffers and precipitants) of the crystallization solutions in the wells of a 24 well tissue culture plate. These concentrations are produced by pipetting the appropriate volume of stock solutions into the wells of the microtiter plate. To design the matrix, the crystallographer decides on an upper and lower concentration of the component. These upper and lower concentrations can be pipetted along either the rows (e.g., A1-A6, B1-B6, C1-C6 or D1-D6) or along the entire tray (A1-D6). The former method is useful for checking reproducibility of crystal growth of a single component along a limited number of wells, whereas the later method is more useful in initial screening. The results of several stages of refinement of the crystallization matrix are illustrated by a representation of three plates. The increase in shading in the wells indicates a positive crystallization result which, in the final stages, would be X-ray quality crystals but in the initial stages could be oil droplets, granular precipitates or small crystals approximately less than 0.05 mm in size. Part A represents an initial screen of one parameter in which the range of concentration between the first well (A1) and last well (D6) is large and the concentration increase between wells is calculated as $((\text{concentration A1}) - (\text{concentration D6})) / 23$. Part B represents that in later stages of the crystallization matrix refinement of the concentration spread between A1 and D6 would be reduced which would result in more crystals formed per plate. Part C indicates a final stage of matrix refinement in which quality crystals are found in most wells of the plate.

Detailed Description of the Invention

[0057] The present invention grows out of the discovery of the three dimensional structure of G-CSF. This three dimensional structure has been expressed via computer program for stereoscopic viewing. By viewing this stereoscopically, structure-function relationships identified and G-CSF analogs have been designed and made.

The Overall Three Dimensional Structure of G-CSF

[0058] The G-CSF used to ascertain the structure was a non-glycosylated 174 amino acid species having an extra N-terminal methionine residue incident to bacterial expression. The DNA and amino acid sequence of this G-CSF are illustrated in FIGURE 1.

[0059] Overall, the three dimensional structure of G-CSF is predominantly helical, with 103 of the 175 residues forming a 4-alpha-helical bundle. The only other secondary structure is found in the loop between the first two long helices where a 4 residue 3^{10} helix is immediately followed by a 6 residue alpha helix. As shown in FIGURE 2, the overall structure has been compared with the structure reported for other proteins: growth hormone (Abdel-Meguid et al., PNAS-USA 84: 6434 (1987) and Vos et al., Science 255: 305-312 (1992)), granulocyte macrophage colony stimulating factor (Diederichs et al., Science 254: 1779-1782 (1991), interferon- β (Senda et al., EMBO J. 11: 3193-3201 (1992)), interleukin-2 (McKay Science 257: 1673-1677 (1992)) and interleukin-4 (Powers et al., Science 256: 1673-1677 (1992), and Smith et al., J. Mol. Biol. 224: 899-904 (1992)). Structural similarity among these growth factors occurs despite the absence of similarity in their amino acid sequences.

[0060] Presently, the structural information was correlation of G-CSF biochemistry, and this can be summarized as follows (with sequence position 1 being at the N-terminus):

Sequence Position	Description of Structure	Analysis
1-10	Extended chain	Deletion causes no loss of biological activity
Cys 18	Partially buried	Reactive with DTNB and Thimersosol but not with iodo-acetate
34	Alternative splice site	Insertion reduces biological activity
20-47 (inclusive)	Helix A, first disulfide and portion of AB helix	Predicted receptor binding region based on neutralizing antibody data
20, 23, 24	Helix A	Single alanine mutation of residue(s) reduces biological activity. Predicted receptor binding (Site B).
165-175 (inclusive)	Carboxy terminus	Deletion reduces biological activity

[0061] This biochemical information, having been gleaned from antibody binding studies, see Layton et al., Biochemistry 266: 23815-23823 (1991), was superimposed on the three-dimensional structure in order to design G-CSF analogs. The design, preparation, and testing of these G-CSF analogs is described in Example 1 below.

EXAMPLE 1

[0062] This Example describes the preparation of crystalline G-CSF, the visualization of the three dimensional structure of recombinant human G-CSF via computer-generated image, the preparation of analogs, using site-directed mutagenesis or nucleic acid amplification methods, the biological assays and HPLC analysis used to analyze the G-CSF analogs, and the resulting determination of overall structure/function relationships. All cited publications are herein incorporated by reference.

A. Use of Automated Crystallization

[0063] The need for a three-dimensional structure of recombinant human granulocyte colony stimulating factor (r-hu-G-CSF), and the availability of large quantities of the purified protein, led to methods of crystal growth by incomplete factorial sampling and seeding. Starting with the implementation of incomplete factorial crystallization described by Jancarik and Kim, J. Appl. Crystallogr. 24: 409 (1991) solution conditions that yielded oil droplets and birefringence aggregates were ascertained. Also, software and hardware of an automated pipetting system were modified to produce some 400 different crystallization conditions per day. Weber, J. Appl. Crystallogr. 20: 366-373 (1987). This procedure led to a crystallization solution which produced r-hu-G-CSF crystals.

[0064] The size, reproducibility and quality of the crystals was improved by a seeding method in which the number of "nucleation initiating units" was estimated by serial dilution of a seeding solution. These methods yielded reproducible growth of 2.0 mm r-hu-G-CSF crystals. The space group of these crystals is $P2_12_12_1$ with cell dimensions of $a=90$ Å, $b=110$ Å and $c=49$ Å, and they diffract to a resolution of 2.0 Å.

1. Overall Methodology

[0065] To search for the crystallizing conditions of a new protein, Carter and Carter, J. Biol. Chem. 254: 12219-12223 (1979) proposed the incomplete factorial method. They suggested that a sampling of a large number of randomly selected, but generally probable, crystallizing conditions may lead to a successful combination of reagents that produce protein crystallization. This idea was implemented by Jancarik and Kim, J. Appl. Crystallogr. 24: 409(1991), who described 32 solutions for the initial crystallization trials which cover a range of pH, salts and precipitants. Here we describe an extension of their implementation to an expanded set of 70 solutions. To minimize the human effort and error of solution preparation, the method has been programmed for an automatic pipetting machine.

[0066] Following Weber's method of successive automated grid searching (SAGS), J.Cryst. Growth 90: 318-324(1988), the robotic system was used to generate a series of solutions which continually refined the crystallization conditions of temperature, pH, salts and precipitant. Once a solution that could reproducibly grow crystals was determined, a seeding technique which greatly improved the quality of the crystals was developed. When these methods were combined, hundreds of diffraction quality crystals (crystals diffracting to at least about 2.5 Angstroms, preferably having at least portions diffracting to below 2 Angstroms, and more preferably, approximately 1 Angstrom) were produced in a few days.

[0067] Generally, the method for crystallization, which may be used with any protein one desires to crystallize, comprises the steps of:

- (a) combining aqueous aliquots of the desired protein with either (i) aliquots of a salt solution, each aliquot having a different concentration of salt; or (ii) aliquots of a precipitant solution, each aliquot having a different concentration of precipitant, optionally wherein each combined aliquot is combined in the presence of a range of pH;
- (b) observing said combined aliquots for precrystalline formations, and selecting said salt or precipitant combination and said pH which is efficacious in producing precrystalline forms, or, if no precrystalline forms are so produced, increasing the protein starting concentration of said aqueous aliquots of protein;
- (c) after said salt or said precipitant concentration is selected, repeating step (a) with said previously unselected solution in the presence of said selected concentration; and
- (d) repeating step (b) and step (a) until a crystal of desired quality is obtained.

[0068] The above method may optionally be automated, which provides vast savings in time and labor. Preferred protein starting concentrations are between 10mg/ml and 20mg/ml, however this starting concentration will vary with the protein (the G-CSF below was analyzed using 33mg/ml). A preferred range of salt solution to begin analysis with is

(NaCl) of 0-2.5M. A preferred precipitant is polyethylene glycol 8000, however, other precipitants include organic solvents (such as ethanol), polyethylene glycol molecules having a molecular weight in the range of 500-20,000, and other precipitants known to those skilled in the art. The preferred pH range is pH 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, and 9.0. Precrystallization forms include oils, birefringement precipitants, small crystals (< approximately 0.05 mm), medium crystals (approximately 0.5 to .5 mm) and large crystals (> approximately 0.5 mm). The preferred time for waiting to see a crystalline structure is 48 hours, although weekly observation is also preferred, and generally, after about one month, a different protein concentration is utilized (generally the protein concentration is increased). Automation is preferred, using the Accuflex system as modified. The preferred automation parameters are described below.

[0069] Generally, protein with a concentration between 10 mg/ml and 20 mg/ml was combined with a range of NaCl solutions from 0-2.5 M, and each such combination was performed (separately) in the presence of the above range of concentrations. Once a precrystallization structure is observed, that salt concentration and pH range are optimized in a separate experiment, until the desired crystal quality is achieved. Next, the precipitant concentration, in the presence of varying levels of pH is also optimized. When both are optimized, the optimal conditions are performed at once to achieve the desired result (this is diagrammed in FIGURE 6).

a. Implementation of an automated pipetting system

[0070] Drops and reservoir solutions were prepared by an Accuflex pipetting system (ICN Pharmaceuticals, Costa Mesa, CA) which is controlled by a personal computer that sends ASCII codes through a standard serial interface. The pipetter samples six different solutions by means of a rotating valve and pipettes these solutions onto a plate whose translation in a x-y coordinate system can be controlled. The vertical component of the system manipulates a syringe that is capable both of dispensing and retrieving liquid.

[0071] The software provided with the Accuflex was based on the SAGS method as proposed by Cox and Weber, J.Appl. Crystallogr. 20: 366-373 (1987). This method involves the systematic variation of two major crystallization parameters, pH and precipitant concentration, with provision to vary two others. While building on these concepts, the software used here provided greater flexibility in the design and implementation of the crystallization solutions used in the automated grid searching strategy. As a result of this flexibility the present software also created a larger number of different solutions. This is essential for the implementation of the incomplete factorial method as described in that section below.

[0072] To improve the speed and design of the automated grid searching strategy, the Accuflex pipetting system required software and hardware modifications. The hardware changes allowed the use of two different micro-titer trays, one used for handing drop and one used for sitting drop experiments, and a Plexiglas tray which held 24 additional buffer, salt and precipitant solutions. These additional solutions expanded the grid of crystallizing conditions that could be surveyed.

[0073] To utilize the hardware modifications, the pipetting software was written in two subroutines; one subroutine allows the crystallographer to design a matrix of crystallization solutions based on the concentrations of their components and the second subroutine to translate these concentrations into the computer code which pipettes the proper volumes of the solutions into the crystallization trays. The concentration matrices can be generated by either of two programs. The first program (MRF, available from Amgen, Inc., Thousand Oaks, CA) refers to a list of stock solution concentrations supplied by the crystallographer and calculates the required volume to be pipette to achieve the designated concentration. The second method, which is preferred, incorporates a spread sheet program (Lotus) which can be used to make more sophisticated gradients of precipitants or pH. The concentration matrix created by either program is interpreted by the control program (SUX, a modification of the program found in the Accuflex pipetter originally and available from Amgen, Inc., Thousand Oaks, CA) and the wells are filled accordingly.

b. Implementation of the Incomplete Factorial Method

[0074] The convenience of the modified pipetting system for preparing diverse solutions improved the implementation of an expanded incomplete factorial method. The development of a new set of crystallization solutions having "random" components was generated using the program INFAC, Carter et al., J.Cryst. Growth 90: 60-73(1988) which produced a list containing 96 random combinations of one factor from three variables. Combinations of calcium and phosphate which immediately precipitated were eliminated, leaving 70 distinct combinations of precipitants, salts and buffers. These combinations were prepared using the automated pipetter and incubated for 1 week. The mixtures were inspected and solutions which formed precipitants were prepared again with lower concentrations of their components. This was repeated until all wells were clear of precipitant.

c. Crystallization of r-hu-G-CSF

[0075] Several different crystallization strategies were used to find a solution which produced x-ray quality crystals. These strategies included the use of the incomplete factorial method, refinement of the crystallization conditions using successive automated grid searches (SAGS), implementation of a seeding technique and development of a crystal production procedure which yielded hundreds of quality crystals overnight. Unless otherwise noted the screening and production of r-hu-G-CSF crystals utilized the hanging drop vapor diffusion method. Afinsen et al., Physical principles of protein crystallization. In: Eisenberg (ed.), Advances in Protein Chemistry 41: 1-33 (1991).

[0076] The initial screening for crystallization conditions of r-hu-G-CSF used the Jancarik and Kim, J. Appl. Crystallogr. 24: 409(1991) incomplete factorial method which resulted in several solutions that produced "preciprecrystallization" results. These results included birefringent precipitants, oils and very small crystals (< .05 mm). These preciprecrystallization solutions then served as the starting points for systematic screening.

[0077] The screening process required the development of crystallization matrices. These matrices corresponded to the concentration of the components in the crystallization solutions and were created using the IBM-PC based spread sheet Lotus™ and implemented with the modified Accuflex pipetting system. The strategy in designing the matrices was to vary one crystallization condition (such as salt concentration) while holding the other conditions such as pH, and precipitant concentration constant. At the start of screening, the concentration range of the varied condition was large but the concentration was successively refined until all wells in the micro-titer tray produced the same crystallization result. These results were scored as follows: crystals, birefringement precipitate, granular precipitate, oil droplets and amorphous mass. If the concentration of a crystallization parameter did not produce at least a precipitant, the concentration of that parameter was increased until a precipitant formed. After each tray was produced, it was left undisturbed for at least two days and then inspected for crystal growth. After this initial screening, the trays were then inspected on a weekly basis.

[0078] From this screening process, two independent solutions with the same pH and precipitant but differing in salts (MgCl₂, LiSO₄) were identified which produced small (0.1 x 0.05 x 0.05 mm) crystals. Based on these results, a new series of concentration matrices were produced which varied MgCl₂ with respect to LiSO₄ while keeping the other crystallization parameters constant. This series of experiments resulted in identification of a solution which produced diffraction quality crystals (> approximately 0.5 mm) in about three weeks. To find this crystallization growth solution (100 mM Mes pH 5.8, 380 mM MgCl₂, 220 mM LiSO₄ and 8% PEG 8k) approximately 8,000 conditions had been screened which consumed about 300 mg of protein.

[0079] The size of the crystals depended on the number of crystals forming per drop. Typically 3 to 5 crystals would be formed with average size of (1.0 x 0.7 x 0.7 mm). Two morphologies which had an identical space group (P2₁2₁2₁) and unit cell dimensions a=90.2, b=110.2, c=49.5 were obtained depending on whether or not seeding (see below) was implemented. Without seeding, the r-hu-G-CSF crystals had one long flat surface and rounded edges.

[0080] When seeding was employed, crystals with sharp faces were observed in the drop within 4 to 6 hours (0.05 by 0.05 by 0.05 mm). Within 24 hours, crystals had grown to (0.7 by 0.7 by 0.7 mm) and continued to grow beyond 2 mm depending on the number of crystals forming in the drop.

d. Seeding and determination of nucleation initiation sites.

[0081] The presently provided method for seeding crystals establishes the number of nucleation initiation units in each individual well used (here, after the optimum conditions for growing crystals had been determined). The method here is advantageous in that the number of "seeds" affects the quality of the crystals, and this in turn affects the degree of resolution. The present seeding here also provides advantages in that with seeding, G-CSF crystal grows in a period of about 3 days, whereas without seeding, the growth takes approximately three weeks.

[0082] In one series of production growth (see methods), showers of small but well defined crystals were produced overnight (<0.01 x 0.01 x 0.01 mm). Crystallization conditions were followed as described above except that a pipette tip employed in previously had been reused. Presumably, the crystal showering effect was caused by small nucleation units which had formed in the used tip and which provided sites of nucleation for the crystals. Addition of a small amount (0.5 ul) of the drops containing the crystal showers to a new drop under standard production growth conditions resulted in a shower of crystals overnight. This method was used to produce several trays of drops containing crystal showers which we termed "seed stock".

[0083] The number of nucleation initiation units (NIU) contained within the "seed stock" drops was estimated to attempt to improve the reproducibility and quality of the r-hu-G-CSF crystals. To determine the number of NIU in the "seed stock", an aliquot of the drop was serially diluted along a 96 well microtiter plate. The microtiter plate was prepared by adding 50 ul of a solution containing equal volumes of r-hu-G-CSF (33 mg/ml) and the crystal growth solution (described above) in each well. An aliquot (3 ul) of one of the "seed stock" drops was transferred to the first well of the microtiter plate. The solution in the well was mixed and 3 ul was then transferred to the next well along the row of the

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microtiter plate. Each row of the microtiter plate was similarly prepared and the tray was sealed with plastic tape. Overnight, small crystals formed in the bottom of the wells of the microtiter plate and the number of crystals in the wells were correlated to the dilution of the original "seed stock". To produce large single crystals, the "seed stock" drop was appropriately diluted into fresh CGS and then an aliquot of this solution containing the NIU was transferred to a drop

5 [0084] Once crystallization conditions had been optimized, crystals were grown in a production method in which 3 ml each of CGS and r-hu-G-CSF (33 mg/ml) were mixed to create 5 trays (each having 24 wells). This method included the production of the refined crystallization solution in liter quantities, mixing this solution with protein and placing the protein/crystallization solution in either hanging drop or sitting drop trays. This process typically yielded 100 to 300 quality crystals (>0.5 mm) in about 5 days.

10 e. Experimental Methods

Materials

15 [0085] Crystallographic information was obtained starting with r-hu-met-G-CSF with the amino acid sequence as provided in FIGURE 1 with a specific activity of $1.0 \pm 0.6 \times 10^8$ U/mg (as measured by cell mitogenesis assay in a 10 mM acetate buffer at pH 4.0 (in Water for Injection) at a concentration of approximately 3 mg/ml solution was concentrated with an Amicon concentrator at 75 psi using a YM10 filter. The solution was typically concentrated 10 fold at 4°C and stored for several months.

20 Initial Screening

[0086] Crystals suitable for X-ray analysis were obtained by vapor-diffusion equilibrium using hanging drops. For preliminary screening, 7 μ l of the protein solution at 33 mg/ml (as prepared above) was mixed with an equal volume of the well solution, placed on siliconized glass plates and suspended over the well solution utilizing Linbro tissue culture plates (Flow Laboratories, McLean, Va). All of the pipetting was performed with the Accuflex pipetter, however, trays were removed from the automated pipetter after the well solutions had been created and thoroughly mixed for at least 10 minutes with a table top shaker. The Linbro trays were then returned to the pipetter which added the well and protein solutions to the siliconized cover slips. The cover slips were then inverted and sealed over 1 ml of the well solutions with silicon grease.

30 [0087] The components of the automated crystallization system are as follows. A PC-DOS computer system was used to design a matrix of crystallization solutions based on the concentration of their components. These matrices were produced with either MRF of the Lotus spread sheet (described above). The final product of these programs is a data file. This file contains the information required by the SUX program to pipette the appropriate volume of the stock solutions to obtain the concentrations described in the matrices. The SUX program information was passed through a serial I/O port and used to dictate to the Accuflex pipetting system the position of the valve relative to the stock solutions, the amount of solution to be retrieved, and then pipetted into the wells of the microtiter plates and the X-Y position of each well (the column/row of each well). Addition information was transmitted to the pipetter which included the Z position (height) of the syringe during filling as well as the position of a drain where the system pauses to purge the syringe between fillings of different solutions. The 24 well microtiter plate (either Linbro or Cryschem) and cover slip holder was placed on a plate which was moved in the X-Y plane. Movement of the plate allowed the pipetter to position the syringe to pipette into the wells. It also positioned the coverslips and vials and extract solutions from these sources. Prior the pipetting, the Linbro microtiter plates had a thin film of grease applied around the edges of the wells. After the crystallization solutions were prepared in the wells and before they were transferred to the cover slips, the microtiter plate was removed from the pipetting system, and solutions were allowed to mix on a table top shaker for ten minutes. After mixing, the well solution was either transferred to the cover slips (in the case of the hanging drop protocol) or transferred to the middle post in the well (in the case of the sitting drop protocol). Protein was extracted from a vial and added to the coverslip drop containing the well solution (or to the post). Plastic tape was applied to the top of the Cryschem plate to seal the wells.

50 Production Growth

55 [0088] Once conditions for crystallization had been optimized, crystal growth was performed utilizing a "production" method. The crystallization solution which contained 100 mM Mes pH 5.8, 380 mM MgCl₂, 220 mM LiSO₄, and 8% PEG 8K was made in 1 liter quantities. Utilizing an Eppendorf syringe pipetter, 1 ml aliquots of this solution were pipetted into each of the wells of the Linbro plate. A solution containing 50% of this solution and 50% G-CSF (33 mg/ml) was mixed and pipetted onto the siliconized cover slips. Typical volumes of these drops were between 50 and 100 μ l and because of the large size of these drops, great care was taken in flipping the coverslips and suspending the drops over

the wells.

Data Collection

[0089] The structure has been refined with X-PLOR (Bruniger, X-PLOR version 3.0, A system for crystallography and NMR, Yale University, New Haven CT) against 2.2Å data collected on an R-AXIS (Molecular Structure, Corp. Houston, TX) imaging plate detector.

f. Observations

[0090] As an effective recombinant human therapeutic, r-hu-G-CSF has been produced in large quantities and gram levels have been made available for structural analysis. The crystallization methods provided herein are likely to find other applications as other proteins of interest become available. This method can be applied to any crystallographic project which has large quantities of protein (approximately >200 mg). As one skilled in the art will recognize, the present materials and methods may be modified and equivalent materials and methods may be available for crystallization of other proteins.

B. Computer Program For Visualizing The Three Dimensional Structure of G-CSF

[0091] Although diagrams, such as those in the Figures herein, are useful for visualizing the three dimensional structure of G-CSF, a computer program which allows for stereoscopic viewing of the molecule is contemplated as preferred. This stereoscopic viewing, or "virtual reality" as those in the art sometimes refer to it, allows one to visualize the structure in its three dimensional form from every angle in a wide range of resolution, from macromolecular structure down to the atomic level. The computer programs contemplated herein also allow one to change perspective of the viewing angle of the molecule, for example by rotating the molecule. The contemplated programs also respond to changes so that one may, for example, delete, add, or substitute one or more images of atoms, including entire amino acid residues, or add chemical moieties to existing or substituted groups, and visualize the change in structure.

[0092] Other computer based systems may be used; the elements being: (a) a means for entering information, such as orthogonal coordinates or other numerically assigned coordinates of the three dimensional structure of G-CSF; (b) a means for expressing such coordinates, such as visual means so that one may view the three dimensional structure and correlate such three dimensional structure with the composition of the G-CSF molecule, such as the amino acid composition; (c) optionally, means for entering information which alters the composition of the G-CSF molecule expressed, so that the image of such three dimensional structure displays the altered composition.

[0093] The coordinates for the preferred computer program used are presented in FIGURE 5. The preferred computer program is Insight II, version 4, available from Biosym in San Diego, CA. For the raw crystallographic structure, the observed intensities of the diffraction data ("F-obs") and the orthogonal coordinates are also deposited in the Protein Data Bank, Chemistry Department, Brookhaven National Laboratory, Upton, New York 19723, USA and these are herein incorporated by reference.

[0094] Once the coordinates are entered into the Insight II program, one can easily display the three dimensional G-CSF molecule representation on a computer screen. The preferred computer system for display is Silicon Graphics 320 VGX (San Diego, CA). For stereoscopic viewing, one may wear eyewear (Crystal Eyes, Silicon Graphics) which allows one to visualize the G-CSF molecule in three dimensions stereoscopically, so one may turn the molecule and envision molecular design.

[0095] Thus, the present invention provides a method of designing or preparing a G-CSF analog with the aid of a computer comprising:

- (a) providing said computer with the means for displaying the three dimensional structure of a G-CSF molecule including displaying the composition of moieties of said G-CSF molecule, preferably displaying the three dimensional location of each amino acid, and more preferably displaying the three dimensional location of each atom of a G-CSF molecule;
- (b) viewing said display;
- (c) selecting a site on said display for alteration in the composition of said molecule or the location of a moiety; and
- (d) preparing a G-CSF analog with such alteration.

[0096] The alteration may be selected based on the desired structural characteristics of the end-product G-CSF analog, and considerations for such design are described in more detail below. Such considerations include the location and compositions of hydrophobic amino acid residues, particularly residues internal to the helical structures of a G-CSF molecule which residues, when altered, alter the overall structure of the internal core of the molecule and may prevent

receptor binding; the location and compositions of external loop structures, alteration of which may not affect the overall structure of the G-CSF molecule.

[0097] FIGURES 2-4 illustrate the overall three dimensional conformation in different ways. The topological diagram, the ribbon diagram, and the barrel diagram all illustrate aspects of the conformation of G-CSF.

[0098] FIGURE 2 illustrates a comparison between G-CSF and other molecules. There is a similarity of architecture, although these growth factors differ in the local conformations of their loops and bundle geometrics. The up-up-down-down topology with two long crossover connections is conserved, however, among all six of these molecules, despite the dissimilarity in amino acid sequence.

[0099] FIGURE 3 illustrates in more detail the secondary structure of recombinant human G-CSF. This ribbon diagram illustrates the handedness of the helices and their positions relative to each other.

[0100] FIGURE 4 illustrates in a different way the conformation of recombinant human G-CSF. This "barrel" diagram illustrates the overall architecture of recombinant human G-CSF.

C. Preparation of Analogs Using M13 Mutagenesis

[0101] This example relates to the preparation of G-CSF analogs using site directed mutagenesis techniques involving the single stranded bacteriophage M13, according to methods published in PCT Application No. WO 85/00817 (Souza et al., published February 28, 1985, herein incorporated by reference). This method essentially involves using a single-stranded nucleic acid template of the non-mutagenized sequence, and binding to it a smaller oligonucleotide containing the desired change in the sequence. Hybridization conditions allow for non-identical sequences to hybridize and the remaining sequence is filled in to be identical to the original template. What results is a double stranded molecule, with one of the two strands containing the desired change. This mutagenized single strand is separated, and used itself as a template for its complementary strand. This creates a double stranded molecule with the desired change.

[0102] The original G-CSF nucleic acid sequence used is presented in FIGURE 1, and the oligonucleotides containing the mutagenized nucleic acid(s) are presented in Table 2. Abbreviations used herein for amino acid residues and nucleotides are conventional, see Stryer, Biochemistry, 3d Ed., W.H. Freeman and Company, N.Y., N.Y. 1988, inside back cover.

[0103] The original G-CSF nucleic acid sequence was first placed into vector M13mp21. The DNA from single stranded phage M13mp21 containing the original G-CSF sequence was then isolated, and resuspended in water. For each reaction, 200 ng of this DNA was mixed with a 1.5 pmole of phosphorylated oligonucleotide (Table 2) and suspended in 0.1M Tris, 0.01M MgCl₂, 0.005M DTT, 0.1mM ATP, pH 8.0. The DNAs were annealed by heating to 65°C and slowly cooling to room temperature.

[0104] Once cooled, 0.5mM of each ATP, dATP, dCTP, dGTP, TTP, 1 unit of T4 DNA ligase and 1 unit of Klenow fragment of *E. coli* polymerase 1 were added to the 1 unit of annealed DNA in 0.1M Tris, 0.025M NaCl, 0.01M MgCl₂, 0.01M DTT, pH 7.5.

[0105] The now double stranded, closed circular DNA was used to transfect *E. coli* without further purification. Plaques were screened by lifting the plaques with nitrocellulose filters, and then hybridizing the filters with single stranded DNA end-labeled with P³² for 1 hour at 55-60°C. After hybridization, the filters were washed at 0-3°C below the melt temperature of the oligo (2°C for A-T, 4°C for G-C) which selectively left autoradiography signals corresponding to plaques with phage containing the mutated sequence. Positive clones were confirmed by sequencing.

[0106] Set forth below are the oligonucleotides used for each G-CSF analog prepared via the M13 mutagenesis method. The nomenclature indicates the residue and the position of the original amino acid (e.g., Lysine at position 17), and the residue and position of the substituted amino acid (e.g., arginine 17). A substitution involving more than one residue is indicated via superscript notation, with commas between the noted positions or a semicolon indicating different residues. Deletions with no substitutions are so noted. The oligonucleotide sequences used for M13-based mutagenesis are next indicated; these oligonucleotides were manufactured synthetically, although the method of preparation is not critical, any nucleic acid synthesis method and/or equipment may be used. The length of the oligo is also indicated. As indicated above, these oligos were allowed to contact the single stranded phage vector, and then single nucleotides were added to complete the G-CSF analog nucleic acid sequence.

Table 2

<u>G-CSE ANALOGS</u>	<u>SEQUENCES (5' -> 3')</u>	<u>Length (nucleotides)</u>	<u>Seq. ID</u>
Lys17->Arg17	CTT TCT GCT GCG TTG TCT GGA ACA	24	3
Lys24->Arg24	ACA GGT TCG TCG TAT CCA GGG TG	23	4
Lys35->Arg35	CAC TGC AAG AAC GTC TGT GCG CT	23	5
Lys41->Arg41	CGC TAC TTA CCG TCT GTG CCA TC	23	6
Lys17, 24, 35-> Arg17, 24, 35	CTT TCT GCT GCG TTG TCT GGA ACA ACA GGT TCG TCG TAT CCA GGG TG CAC TGC AAG AAC GTC TGT GCG CT	24 23 23	7 8 9
Lys17, 24, 41-> Arg17, 24, 41	CTT TCT GCT GCG TTG TCT GGA ACA ACA GGT TCG TCG TAT CCA GGG TG CGC TAC TTA CCG TCT GTC CCA TC	24 23 23	10 11 12
Lys17, 35, 41-> Arg17, 35, 41	CTT TCT GCT GCG TTG TCT GGA ACA CAC TGC AAG AAC GTC TGT GCG CT CGC TAC TTA CCG TCT GTG CCA TC	24 23 23	13 14 15
Lys24, 35, 41-> Arg24, 35, 41	ACA GGT TCG TCG TAT CCA GGG TG CAC TGC AAG AAC GTC TGT GCG CT CGC TAC TTA CCG TCT GTG CCA TC	23 23 23	16 17 18

Table 2 (cont'd)

G-CSE ANALOGS	SEQUENCES (5' → 3')	Length (nucleotide)	Seq. ID
Lys ^{17,24,35,41} → Arg ^{17,24,35,41}	CTT TCT GCT GCG TTG TCT GGA ACA ACA GGT TCG TCG TAT CCA GGG TG CAC TGC AAG AAC GTC TGT GCG CT CGC TAC TTA CCG TCT GTG CCA TC	24 23 23 23	19 20 21 22
Cys ¹⁸ → Ala ¹⁸ Gln ⁶⁸ → Glu ⁶⁸ Cys ^{37,43} → Ser ^{37,43}	TCT GCT GAA AGC TCT GGA ACA GG CTT GTC CAT CTG AAG CTC TTC AG GAA AAA CTG TCC GCT ACT TAC AAA CTG TCC CAT CCG G	23 23 37	23 24 25
Gln ²⁶ → Ala ²⁶ Gln ¹⁷⁴ → Ala ¹⁷⁴	TTC GTA AAA TCG CGG GTG ACG G TCA TCT GGC TGC GCC GTA ATA G	22 22	26 27
Arg ¹⁷⁰ → Ala ¹⁷⁰	CCG TGT TCT GGC TCA TCT GGC T	22	28
Arg ¹⁶⁷ → Ala ¹⁶⁷	GAA GTA TCT TAC GCT GTT CTG CGT	24	29
Deletion 167	GAA GTA TCT TAC TAA GTT CTG CGT C	25	30
Lys ⁴¹ → Ala ⁴¹	CGC TAC TTA CGC ACT GTG CCA T	22	31
His ⁴⁴ → Lys ⁴⁴	CAA ACT GTG CAA GCC GGA AGA G	22	32
Glu ⁴⁷ → Ala ⁴⁷	CAT CCG GAA GCA CTG GTA CTG C	22	33

Table 2 (con't.)

<u>G-CSF ANALOGS</u>	<u>SEQUENCES (5' -> 3')</u>	<u>Length (nucleotide)</u>	<u>Seq. ID</u>
Arg ²³ ->Ala ²³	GGA ACA GGT TGC TAA AAT CCA GG	23	34
Lys ²⁴ ->Ala ²⁴	GAA CAG GTT CGT GCG ATC CAG GGT G	25	35
Glu ²⁰ ->Ala ²⁰	GAA ATG TCT GGC ACA GGT TCG T	22	36
Asp ²⁸ ->Ala ²⁸	TCC AGG GTG CCG GTG CTG C	19	37
Met ¹²⁷ ->Glu ¹²⁷	AAG AGC TCG GTG AGG CAC CAG CT	23	38
Met ¹³⁸ ->Glu ¹³⁸	CTC AAG GTG CTG AGC CGG CAT TC	23	39
Met ¹²⁷ ->Leu ¹²⁷	GAG CTC GGT CTG GCA CCA GC	20	40
Met ¹³⁸ ->Leu ¹³⁸	TCA AGG TGC TCT GCC GGC ATT	21	41
Ser ¹³ ->Ala ¹³	TCT GCC GCA AGC CTT TCT GCT GA	23	42
Lys ¹⁷ ->Ala ¹⁷	CTT TCT GCT GGC ATG TCT GGA ACA	24	43
Gln ¹²¹ ->Ala ¹²¹	CTA TTT GGC AAG CGA TGG AAG AGC	24	44
Glu ¹²⁴ ->Ala ¹²⁴	CAG ATG GAA GCG CTC GGT ATG	21	45

Table 2 (con't.)

G-CSF ANALOGS	SEQUENCES (5' → 3')	Length (nucleotides)	Seq. ID
Met 127, 138 → Leu 127, 138	GAG CTC GGT CTG GCA CCA GC TCA AGG TGC TCT GCC GGC ATT	20 21	46 47
**Glu 20 → Ala 20; Ser 13 → Gly 13	GAA ATG TCT GGC ACA GGT TCG T	22	48

** This analog came about during the preparation of G-CSF analog Glu 20 → Ala 20. As several clones were being sequenced to identify the Glu 20 → Ala 20 analog, the Glu 20 → Ala 20; Ser 13 → Gly 13 analog was identified. This double mutant was the result of an in vitro Klenow DNA polymerase reaction mistake.

D. Preparation of G-CSF Analogs Using DNA Amplification

[0107] This example relates to methods for producing G-CSF analogs using a DNA amplification technique. Essentially, DNA encoding each analog was amplified in two separate pieces, combined, and then the total sequence itself amplified. Depending upon where the desired change in the original G-CSF DNA was to be made, internal primers were used to incorporate the change, and generate the two separate amplified pieces. For example, for amplification of the 5' end of the desired analog DNA, a 5' flanking primer (complementary to a sequence of the plasmid upstream from the G-CSF original DNA) was used at one end of the region to be amplified, and an internal primer, capable of hybridizing to the original DNA but incorporating the desired change, was used for priming the other end. The resulting amplified region stretched from the 5' flanking primer through the internal primer. The same was done for the 3' terminus, using a 3' flanking primer (complementary to a sequence of the plasmid downstream from the G-CSF original DNA) and an internal primer complementary to the region of the intended mutation. Once the two "halves" (which may or may not be equal in size, depending on the location of the internal primer) were amplified, the two "halves" were allowed to connect. Once connected, the 5' flanking primer and the 3' flanking primer were used to amplify the entire sequence containing the desired change.

[0108] If more than one change is desired, the above process may be modified to incorporate the change into the internal primer, or the process may be repeated using a different internal primer. Alternatively, the gene amplification process may be used with other methods for creating changes in nucleic acid sequence, such as the phage based mutagenesis technique as described above. Examples of process for preparing analogs with more than one change are described below.

[0109] To create the G-CSF analogs described below, the template DNA used was the sequence as in FIGURE 1 plus certain flanking regions (from a plasmid containing the G-CSF coding region). These flanking regions were used as the 5' and 3' flanking primers and are set forth below. The amplification reactions were performed in 40 μ l volumes containing 10 mM Tris-HCl, 1.5 mM MgCl₂, 50 mM KCl, 0.1 mg/ml gelatin, pH 8.3 at 20°C. The 40 μ l reactions also contained 0.1mM of each dNTP, 10 pmoles of each primer, and 1 ng of template DNA. Each amplification was repeated for 15 cycles. Each cycle consisted of 0.5 minutes at 94°C, 0.5 minutes at 50°C, and 0.75 minutes at 72°C. Flanking primers were 20 nucleotides in length and internal primers were 20 to 25 nucleotides in length. This resulted in multiple copies of double stranded DNA encoding either the front portion or the back portion of the desired G-CSF analog.

[0110] For combining the two "halves," one fortieth of each of the two reactions was combined in a third DNA amplification reaction. The two portions were allowed to anneal at the internal primer location, as their ends bearing the mutation were complementary, and following a cycle of polymerization, give rise to a full length DNA sequence. Once so annealed, the whole analog was amplified using the 5' and 3' flanking primers. This amplification process was repeated for 15 cycles as described above.

[0111] The completed, amplified analog DNA sequence was cleaved with XbaI and XhoI restriction endonuclease to produce cohesive ends for insertion into a vector. The cleaved DNA was placed into a plasmid vector, and that vector was used to transform *E. coli*. Transformants were challenged with kanamycin at 50 μ g/ml and incubated at 30°C. Production of G-CSF analog protein was confirmed by polyacrylamide gel electrophoresis of a whole cell lysate. The presence of the desired mutation was confirmed by DNA sequence analysis of plasmid purified from the production isolate. Cultures were then grown, and cells were harvested, and the G-CSF analogs were purified as set forth below.

[0112] Set forth below in Table 3 are the specific primers used for each analog made using gene amplification.

Table 3

Analog Seq. ID	Internal Primer(5'→3')	
His ⁴⁴ →Ala ⁴⁴	5'primer-TTCCGGAGCGCACAGTTTG	49
	3'primer-CAAACGTGTGGGCTCCGGAAGAGC	50
Thr ¹¹⁷ →Ala ¹¹⁷	5'primer-ATGCCAAATTGCAGTAGCAAAG	51
	3'primer-CTTTGCTACTGCAATTTGGCAACA	52
Asp ¹¹⁰ →Ala ¹¹⁰	5'primer-ATCAGCTACTGCTAGCTGCAGA	53
	3'primer-TCTGCAGCTAGCAGTAGCTGACT	54
Gln ²¹ →Ala ²¹	5'primer-TTACGAACCGCTTCCAGACATT	55
	3'primer-AATGTCTGGAAGCGGTTCGTAAAT	56

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Table 3 (continued)

Analog Seq. ID	Internal Primer(5'→3')	
Asp ¹¹³ →Ala ¹¹³	5'primer-GTAGCAAATGCAGCTACATCTA	57
	3'primer-TAGATGTAGCTGCATTGCTACTAC	58
His ⁵³ →Ala ⁵³	5'primer-CCAAGAGAAGCACCCAGCAG	59
	3'primer-CTGCTGGGTGCTTCTCTTGGGA	60
For each analog, the following 5' flanking primer was used:		
	5'-CACTGGCGGTGATAATGAGC	61
For each analog, the following 3' flanking primer was used:		
	3'-GGTCATTACGGACCGGATC	62

1. Construction of Double Mutation

[0113] To make G-CSF analog Gln^{12,21}→Glu^{12,21}, two separate DNA amplifications were conducted to create the two DNA mutations. The template DNA used was the sequence as in FIGURE 1 plus certain flanking regions (from a plasmid containing the G-CSF coding region). The precise sequences are listed below. Each of the two DNA amplification reactions were carried out using a Perkin Elmer/Cetus DNA Thermal Cycler. The 40 ul reaction mix consisted of 1X PCR Buffer (Cetus), 0.2 mM each of the 4 dNTPs (Cetus), 50 pmoles of each primer oligonucleotide, 2 ng of G-CSF template DNA (on a plasmid vector), and 1 unit of Taq polymerase (Cetus). The amplification process was carried out for 30 cycles. Each cycle consisted of 1 minute at 94°C, 2 minutes at 50°C, and 3 minutes at 72°C.

[0114] DNA amplification "A" used the oligonucleotides:

5' CCACTGGCGGTGATACTGAGC 3' (Seq. ID 63) and
5' AGCAGAAAGCTTTCGGCAGAGAAGAAGCAGGA 3' (Seq. ID 64)

[0115] DNA amplification "B" used the oligonucleotides:

5' GCCGCAAAGCTTCTGCTGAAATGTCTGGAAGAGGTTGTAATCCAGGGTGA 3' (Seq. ID 65) and
5' CTGGAATGCAGAAGCAAATGCCGCGATAGCACCTTCAGTCGGTTGCAGAGCTGGTGCCA 3' (Seq. ID 66)

[0116] From the 109 base pair double stranded DNA product obtained after DNA amplification "A", a 64 base pair XbaI to HindIII DNA fragment was cut and isolated that contained the DNA mutation Gln¹²→Glu¹². From the 509 base pair double stranded DNA product obtained after DNA amplification "B", a 197 base pair HindIII to BsmI DNA fragment was cut and isolated that contained the DNA mutation Gln²¹→Glu²¹.

[0117] The "A" and "B" fragments were ligated together with a 4.8 kilo-base pair XbaI to BsmI DNA plasmid vector fragment. The ligation mix consisted of equal molar DNA restriction fragments, ligation buffer (25 mM Tris-HCl pH 7.8, 10 mM MgCl₂, 2 mM DTT, 0.5 mM rATP, and 100 ug/ml BSA) and T4 DNA ligase and was incubated overnight at 14°C. The ligated DNA was then transformed into *E. coli* FM5 cells by electroporation using a Bio Rad Gene Pulsar apparatus (BioRad, Richmond, CA). A clone was isolated and the plasmid construct verified to contain the two mutations by DNA sequencing. This 'intermediate' vector also contained a deletion of a 193 base pair BsmI to BsmI DNA fragment. The final plasmid vector was constructed by ligation and transformation (as described above) of DNA fragments obtained by cutting and isolating a 2 kilo-base pair SstI to BamHI DNA fragment from the intermediate vector, a 2.8 kbp SstI to EcoRI DNA fragment from the plasmid vector, and a 360 bp BamHI to EcoRI DNA fragment from the plasmid vector. The final construct was verified by DNA sequencing the G-CSF gene. Cultures were grown, and the cells were harvested, and the G-CSF analogs were purified as set forth below.

[0118] As indicated above, any combination of mutagenesis techniques may be used to generate a G-CSF analog nucleic acid (and expression product) having one or more than one alteration. The two examples above, using M13-based mutagenesis and gene amplification-based mutagenesis, are illustrative.

E. Expression of G-CSF Analog DNA

[0119] The G-CSF analog DNAs were then placed into a plasmid vector and used to transform *E. coli* strain FM5 (ATCC#53911). The present G-CSF analog DNAs contained on plasmids and in bacterial host cells are available from the American Type Culture Collection, Rockville, MD, and the accession designations are indicated below.

[0120] One liter cultures were grown in broth containing 10g tryptone, 5g yeast extract and 5g NaCl) at 30°C until reaching a density at A⁶⁰⁰ of 0.5, at which point they were rapidly heated to 42°C. The flasks were allowed to continue shaking at for three hours.

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[0121] Other prokaryotic or eukaryotic host cells may also be used, such as other bacterial cells, strains or species, mammalian cells in culture (COS, CHO or other types) insect cells or multicellular organs or organisms, or plant cells or multicellular organs or organisms, and a skilled practitioner will recognize the appropriate host. The present G-CSF analogs and related compositions may also be prepared synthetically, as, for example, by solid phase peptide synthesis methods, or other chemical manufacturing techniques. Other cloning and expression systems will be apparent to those skilled in the art.

F. Purification of G-CSF Analog Protein

[0122] Cells were harvested by centrifugation (10,000 x G, 20 minutes, 4°C). The pellet (usually 5 grams) was resuspended in 30 ml of 1mM DTT and passed three times through a French press cell at 10,000 psi. The broken cell suspension was centrifuged at 10,000g for 30 minutes, the supernatant removed, and the pellet resuspended in 30-40 ml water. This was recentrifuged at 10,000 x G for 30 minutes, and this pellet was dissolved in 25 ml of 2% Sarkosyl and 50mM Tris at pH 8. Copper sulfate was added to a concentration of 40uM, and the mixture was allowed to stir for at least 15 hours at 15-25°C. The mixture was then centrifuged at 20,000 x G for 30 minutes. The resultant solubilized protein mixture was diluted four-fold with 13.3 mM Tris, pH 7.7, the Sarkosyl was removed, and the supernatant was then applied to a DEAE-cellulose (Whatman DE-52) column equilibrated in 20mM Tris, pH 7.7. After loading and washing the column with the same buffer, the analogs were eluted with 20mM Tris /NaCl (between 35mM to 100mM depending on the analog, as indicated below), pH 7.7. For most of the analogs, the eluent from the DEAE column was adjusted to a pH of 5.4, with 50% acetic acid and diluted as necessary (to obtain the proper conductivity) with 5mM sodium acetate pH 5.4. The solution was then loaded onto a CM-sepharose column equilibrated in 20 mM sodium acetate, pH 5.4. The column was then washed with 20mM NaAc, pH 5.4 until the absorbance at 280 nm was approximately zero. The G-CSF analog was then eluted with sodium acetate/NaCl in concentrations as described below in Table 4. The DEAE column eluents for those analogs not applied to the CM-sepharose column were dialyzed directly into 10mM NaAc, pH 4.0 buffer. The purified G-CSF analogs were then suitably isolated for *in vitro* analysis. The salt concentrations used for eluting the analogs varied, as noted above. Below, the salt concentrations for the DEAE cellulose column and for the CM-sepharose column are listed:

Table 4
Salt Concentrations

<u>Analog</u>	<u>DEAE Cellulose</u>	<u>CM-Sepharose</u>
Lys17->Arg17	35mM	37.5mM
Lys24->Arg24	35mM	37.5mM
Lys35->Arg35	35mM	37.5mM
Lys41->Arg41	35mM	37.5mM
Lys17, 24, 35-	35mM	37.5mM
>Arg17, 24, 35		
Lys17, 35, 41-	35mM	37.5mM
>Arg17, 35, 41		

Table 4 Con't

	<u>Analog</u>	<u>DEAE Cellulose</u>	<u>CM-Sephadrose</u>
5	Lys24, 35, 41-	35mM	37.5mM
	>Arg24, 35, 41		
10	Lys17, 24, 35, 41	35mM	37.5mM
	->Arg17, 24, 35, 41		
	Lys17, 24, 41-	35mM	37.5mM
	>Arg17, 24, 41		
15	Gln68->Glu68	60mM	37.5mM
	Cys37, 43->Ser37, 43	40mM	37.5mM
	Gln26->Ala26	40mM	40mM
20	Gln174->Ala174	40mM	40mM
	Arg170->Ala170	40mM	40mM
	Arg167->Ala167	40mM	40mM
25	Deletion 167*	N/A	N/A
	Lys41->Ala41	160mM	40mM
	His44->Lys44	40mM	60mM
	Glu47->Ala47	40mM	40mM
30	Arg23->Ala23	40mM	40mM
	Lys24->Ala24	120mM	40mM
	Glu20->Ala20	40mM	60mM
35	Asp28->Ala28	40mM	80mM
	Met127->Glu127	80mM	40mM
	Met138->Glu138	80mM	40mM
40	Met127->Leu127	40mM	40mM
	Met138->Leu138	40mM	40mM
	Cys18->Ala18	40mM	37.5mM
45	Gln12, 21->Glu12, 21	60mM	37.5mM
	Gln12, 21, 68-	60mM	37.5mM
	>Glu12, 21, 68		
	Glu20->Ala20;		
50	Ser13		
	->Gly13	40mM	80mM

Table 4 Con't

<u>Analog</u>	<u>DEAE Cellulose</u>	<u>CM-Sephadex</u>
Met ^{127,138} -	40mM	40mM
>Leu ^{127,138}		
Ser ¹³ ->Ala ¹³	40mM	40mM
Lys ¹⁷ ->Ala ¹⁷	80mM	40mM
Gln ¹²¹ ->Ala ¹²¹	40mM	60mM
Gln ²¹ ->Ala ²¹	50mM	Gradient 0 -150mM
His ⁴⁴ ->Ala ⁴⁴ **	40mM	N/A
His ⁵³ ->Ala ⁵³ **	50mM	N/A
Asp ¹¹⁰ ->Ala ¹¹⁰ **	40mM	N/A
Asp ¹¹³ ->Ala ¹¹³ **	40mM	N/A
Thr ¹¹⁷ ->Ala ¹¹⁷ **	50mM	N/A
Asp ²⁸ ->Ala ²⁸ ;	50mM	N/A
Asp ¹¹⁰		
Ala ¹¹⁰ **		
Glu ¹²⁴ ->Ala ¹²⁴ **	40mM	40mM

* For Deletion 167, the data are unavailable.

** For these analogs, the DEAE cellulose column alone was use for purification.

[0123] The above purification methods are illustrative, and a skilled practitioner will recognize that other means are available for obtaining the present G-CSF analogs.

G. Biological Assays

[0124] Regardless of which methods were used to create the present G-CSF analogs, the analogs were subject to assays for biological activity. Tritiated thymidine assays were conducted to ascertain the degree of cell division. Other biological assays, however, may be used to ascertain the desired activity. Biological assays such as assaying for the ability to induce terminal differentiation in mouse WEHI-3B (D+) leukemic cell line, also provides indication of G-CSF activity. See Nicola, et al., Blood 54: 614-27 (1979). Other *in vitro* assays may be used to ascertain biological activity. See Nicola, Annu. Rev. Biochem. 58: 45-77 (1989). In general, the test for biological activity should provide analysis for the desired result, such as increase or decrease in biological activity (as compared to non-altered G-CSF), different biological activity (as compared to non-altered G-CSF), receptor affinity analysis, or serum half-life analysis. The list is incomplete, and those skilled in the art will recognize other assays useful for testing for the desired end result.

[0125] The ³H-thymidine assay was performed using standard methods. Bone marrow was obtained from sacrificed female Balb C mice. Bone marrow cells were briefly suspended, centrifuged, and resuspended in a growth medium. A 160 ul aliquot containing approximately 10,000 cells was placed into each well of a 96 well micro-titer plate. Samples of the purified G-CSF analog(as prepared above) were added to each well, and incubated for 68 hours. Tritiated thymidine was added to the wells and allowed to incubate for 5 additional hours. After the 5 hour incubation time, the cells were harvested, filtered, and thoroughly rinsed. The filters were added to a vial containing scintillation fluid. The beta emissions were counted (LKB Betaplate scintillation counter). Standards and analogs were analyzed in triplicate, and samples which fell substantially above or below the standard curve were re-assayed with the proper dilution.

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The results reported here are the average of the triplicate analog data relative to the unaltered recombinant human G-CSF standard results.

H. HPLC Analysis

[0126] High pressure liquid chromatography was performed on purified samples of analog. Although peak position on a reverse phase HPLC column is not a definitive indication of structural similarity between two proteins, analogs which have similar retention times may have the same type of hydrophobic interactions with the HPLC column as the non-altered molecule. This is one indication of an overall similar structure.

[0127] Samples of the analog and the non-altered recombinant human G-CSF were analyzed on a reverse phase (0.46 x 25 cm) Vydac 214TP54 column (Separations Group, Inc. Hesperia, CA). The purified analog G-CSF samples were prepared in 20 mM acetate and 40 mM NaCl solution buffered at pH 5.2 to a final concentration of 0.1 mg/ml to 5 mg/ml, depending on how the analog performed in the column. Varying amounts (depending on the concentration) were loaded onto the HPLC column, which had been equilibrated with an aqueous solution containing 1% isopropanol, 52.8% acetonitrile, and .38% trifluoro acetate (TFA). The samples were subjected to a gradient of 0.86%/minute acetonitrile, and .002% TFA.

I. Results

[0128] Presented below are the results of the above biological assays and HPLC analysis. Biological activity is the average of triplicate data and reported as a percentage of the control standard (non-altered G-CSF). Relative HPLC peak position is the position of the analog G-CSF relative to the control standard (non-altered G-CSF) peak. The "+" or "-" symbols indicate whether the analog HPLC peak was in advance of or followed the control standard peak (in minutes). Not all of the variants had been analyzed for relative HPLC peak, and only those so analyzed are included below. Also presented are the American Type Culture Collection designations for *E. coli* host cells containing the nucleic acids coding for the present analogs, as prepared above.

Table 5

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal	
					G-CSF	Activity
67	1	Lys17->Arg17	N/A	69184	N/A	N/A
68	2	Lys24->Arg24	N/A	69185	N/A	N/A
69	3	Lys35->Arg35	N/A	69186	N/A	N/A
70	4	Lys41->Arg41	N/A	69187	N/A	N/A
71	5	Lys17, 24, 35->Arg17, 24, 35	N/A	69189	N/A	N/A
72	6	Lys17, 35, 41->Arg17, 35, 41	N/A	69192	N/A	N/A
73	7	Lys24, 35, 41->Arg24, 35, 41	N/A	69191	N/A	N/A
74	8	Lys17, 24, 35, 41 ->Arg17, 24, 35, 41	N/A	69193	N/A	N/A
75	9	Lys17, 24, 41->Arg17, 24, 41	N/A	69190	N/A	N/A
76	10	Gln68->Glu68	N/A	69196	N/A	N/A
77	11	Cys37, 43->Ser37, 43	N/A	69197	N/A	N/A
78	12	Gln26->Ala26	+ .96	69201	51%	51%
79	13	Gln174->Ala174	+ .14	69202	100%	100%
80	14	Arg170->Ala170	+ .78	69203	100%	100%

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal	
					G-CSF	Activity
81	15	Arg167->Ala167	+ .54	69204	110%	
82	16	Deletion 167	- .99	69207	N/A	
83	17	Lys41->Ala41	+ .25	69208	81%	
84	18	His44->Lys44	-1.53	69212	70%	
85	19	Glu47->Ala47	+ .14	69205	0%	
86	20	Arg23->Ala23	- .03	69206	31%	
87	21	Lys24->Ala24	+1.95	69213	0%	
88	22	Glu20->Ala20	-0.07	69211	0%	
89	23	Asp28->Ala28	- .30	69210	147%	
90	24	Met127->Glu127	N/A	69223	N/A	
91	25	Met138->Glu138	N/A	69222	N/A	
92	26	Met127->Leu127	N/A	69198	N/A	
93	27	Met138->Leu138	N/A	69199	N/A	
94	28	Cys18->Ala18	N/A	69188	N/A	
95	29	Gln12,21->Glu12,21	N/A	69194	N/A	
96	30	Gln12,21,68->Glu12,21,68	N/A	69195	N/A	
97	31	Glu20->Ala20; Ser13	+1.74	69209	0%	

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal	
					G-CSF	Activity
98	32	->Gly13				
		Met127,138->Leu127,138	+1.43	69200	98%	
99	33	Ser13->Ala13	0	69221	110%	
100	34	Lys17->Ala17	+0.50	69226	70%	
101	35	Gln121->Ala121	+2.7	69225	100%	
102	36	Gln21->Ala21	+0.63	69217	9.6%	
103	37	His44->Ala44	+1.52	69215	10.8%	
104	38	His53->Ala53	+0.99	69219	8.3%	
105	39	Asp110->Ala110	+1.97	69216	29%	
106	40	Asp113->Ala113	-0.34	69218	0%	
107	41	Thr117->Ala117	+0.4	69214	9.7%	
108	42	Asp28->Ala28; Asp110 Ala110	+3.2	69220	20.6%	

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal	
					G-CSF	Activity
109	43	Glu124->Ala124	+0.16	69224	75%	
110	44	Phe114->Val 114, Thr117->Ala 117**	+0.53		0%	

**This analog was apparently a result of an inadvertent error in the oligo which was used to prepare number 41, above (Thr117->Ala 117), and thus was prepared identically to the process used for that analog.

"N/A" indicates data which are not available.

1. Identification of Structure-Function Relationships

[0129] The first step used to design the present analogs was to determine what moieties are necessary for structural integrity of the G-CSF molecule. This was done at the amino acid residue level, although the atomic level is also available for analysis. Modification of the residues necessary for structural integrity results in change in the overall structure of the G-CSF molecule. This may or may not be desirable, depending on the analog one wishes to produce. The working examples here were designed to maintain the overall structural integrity of the G-CSF molecule, for the purpose of maintain G-CSF receptor binding of the analog to the G-CSF receptor (as used in this section below, the "G-CSF receptor" refers to the natural G-CSF receptor, found on hematopoietic cells). It was assumed, and confirmed by the studies presented here, that G-CSF receptor binding is a necessary step for at least one biological activity, as determined by the above biological assays.

[0130] As can be seen from the figures, G-CSF (here, recombinant human met-G-CSF) is an antiparallel 4-alpha helical bundle with a left-handed twist, and with overall dimensions of 45 Å x 30 Å x 24 Å. The four helices within the bundle are referred to as helices A, B, C and D, and their connecting loops are known as the AB, BC and CD loops. The helix crossing angles range from -167.5° to -159.4°. Helices A, B, and C are straight, whereas helix D contains two kinds of structural characteristics, at Gly 150 and Ser 160 (of the recombinant human met-G-CSF). Overall, the G-CSF molecules is a bundle of four helices, connected in series by external loops. This structural information was then correlated with known functional information. It was known that residues (including methionine at position 1) 47, 23, 24, 20, 21, 44, 53, 113, 110, 28 and 114 may be modified, and the effect on biological activity would be substantial.

[0131] The majority of single mutations which lowered biological activity were centered around two regions of G-CSF that are separated by 30 Å, and are located on different faces of the four helix bundle. One region involves interactions between the A helix and the D helix. This is further confirmed by the presence of salt bridges in the non-altered molecule as follows:

Atom	Helix	Atom	Helix	Distance
Arg 170 N1	D	Tyr 166 OH	A	3.3
Tyr 166 OH	D	Arg 23 N2	A	3.3
Glu 163 OE1	D	Arg 23 N1	A	2.8
Arg 23 N1	A	Gln 26 OE1	A	3.1
Gln 159 NE2	D	Gln 26 O	A	3.3

[0132] Distances reported here were for molecule A, as indicated in FIGURE 5 (wherein three G-CSF molecules crystallized together and were designated as A, B, and C). As can be seen, there is a web of salt bridges between helix A and helix D, which act to stabilize the helix A structure, and therefore affect the overall structure of the G-CSF molecule.

[0133] The area centering around residues Glu 20, Arg 23 and Lys 24 are found on the hydrophilic face of the A helix (residues 20-37). Substitution of the residues with the non-charged alanine residue at positions 20 and 23 resulted in similar HPLC retention times, indicating similarity in structure. Alteration of these sites altered the biological activity (as indicated by the present assays). Substitution at Lys 24 altered biological activity, but did not result in a similar HPLC retention time as the other two alterations.

[0134] The second site at which alteration lowered biological activity involves the AB helix. Changing glutamine at position 47 to alanine (analog no. 19, above) reduced biological activity (in the thymidine uptake assay) to zero. The AB helix is predominantly hydrophobic, except at the amino and carboxy termini; it contains one turn of a 3¹⁰ helix. There are two histidines at each termini (His 44 and His 56) and an additional glutamate at residue 46 which has the potential to form a salt bridge to His 44. The fourier transformed infra red spectrographic analysis (FTIR) of the analog suggests this analog is structurally similar to the non-altered recombinant G-CSF molecule. Further testing showed that this analog would not crystallize under the same conditions as the non-altered recombinant molecule.

[0135] Alterations at the carboxy terminus (Gln 174, Arg 167 and Arg 170) had little effect on biological activity. In contrast, deletion of the last eight residues (167-175) lowered biological activity. These results may indicate that the deletion destabilizes the overall structure which prevents the mutant from proper binding to the G-CSF receptor (and thus initiating signal transduction).

[0136] Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops -- the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the internal hydrophobic residues

are (with methionine being position 1) Phe 14, Cys 18, Val 22, Ile 25, Ile 32 and Leu 36. Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops -- the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the internal hydrophobic residues are (with methionine being position 1 as in FIGURE 1) Phe 14, Cys 18, Val 22, Ile 25, Ile 32 and Leu 36. The other hydrophobic residues (again with the met at position 1) are: helix B, Ala 72, Leu 76, Leu 79, Leu 83, Tyr 86, Leu 90, Leu 93; helix C, Leu 104, Leu 107, Val 111, Ala 114, Ile 118, Met 122; and helix D, Val 154, Val 158, Phe 161, Val 164, Val 168, Leu 172.

[0137] The above biological activity data, from the presently prepared G-CSF analogs, demonstrate that modification of the external loops interfere least with G-CSF overall structure. Preferred loops for analog preparation are the AB loop and the CD loop. The loops are relatively flexible structures as compared to the helices. The loops may contribute to the proteolysis of the molecule. G-CSF is relatively fast acting *in vivo* as the purpose the molecule serves is to generate a response to a biological challenge, i.e., selectively stimulate neutrophils. The G-CSF turnover rate is also relatively fast. The flexibility of the loops may provide a "handle" for proteases to attach to the molecule to inactivate the molecule. Modification of the loops to prevent protease degradation, yet have (via retention of the overall structure of non-modified G-CSF) no loss in biological activity may be accomplished.

[0138] This phenomenon is probably not limited to the G-CSF molecule but may also be common to the other molecules with known similar overall structures, as presented in Figure 2. Alteration of the external loop of, for example hGH, Interferon B, IL-2, GM-CSF and IL-4 may provide the least change to the overall structure. The external loops on the GM-CSF molecule are not as flexible as those found on the G-CSF molecule, and this may indicate a longer serum life, consistent with the broader biological activity of GM-CSF. Thus, the external loops of GM-CSF may be modified by releasing the external loops from the beta-sheet structure, which may make the loops more flexible (similar to those G-CSF) and therefore make the molecule more susceptible to protease degradation (and thus increase the turnover rate).

[0139] Alteration of these external loops may be effected by stabilizing the loops by connection to one or more of the internal helices. Connecting means are known to those in the art, such as the formation of a beta sheet, salt bridge, disulfide bonding or hydrophobic interactions, and other means are available. Also, deletion of one or more moieties, such as one or more amino acid residues or portions thereof, to prepare an abbreviated molecule and thus eliminate certain portions of the external loops may be effected.

[0140] Thus, by alteration of the external loops, preferably the AB loop (amino acids 58-72 of r-hu-met G-CSF) or the CD loop (amino acids 119 to 145 of r-hu-met-G-CSF), and less preferably the amino terminus (amino acids 1-10), one may therefore modify the biological function without elimination of G-CSF receptor binding. For example, one may: (1) increase half-life (or prepare an oral dosage form, for example) of the G-CSF molecule by, for example, decreasing the ability of proteases to act on the G-CSF molecule or adding chemical modifications to the G-CSF molecule, such as one or more polyethylene glycol molecules or enteric coatings for oral formulation which would act to change some characteristic of the G-CSF molecule as described above, such as increasing serum or other half-life or decreasing antigenicity; (2) prepare a hybrid molecule, such as combining G-CSF with part or all of another protein such as another cytokine or another protein which effects signal transduction via entry through the cell through a G-CSF receptor transport mechanism; or (3) increase the biological activity as in, for example, the ability to selectively stimulate neutrophils (as compared to a non-modified G-CSF molecule). This list is not limited to the above exemplars.

[0141] Another aspect observed from the above data is that stabilizing surface interactions may affect biological activity. This is apparent from comparing analogs 23 and 40. Analog 23 contains a substitution of the charged asparagine residue at position 28 for the neutrally-charged alanine residue in that position, and such substitution resulted in a 50% increase in the biological activity (as measured by the disclosed thymidine uptake assays). The asparagine residue at position 28 has a surface interaction with the asparagine residue at position 113; both residues being negatively charged, there is a certain amount of instability (due to the repelling of like charged moieties). When, however the asparagine at position 113 is replaced with the neutrally-charged alanine, the biological activity drops to zero (in the present assay system). This indicates that the asparagine at position 113 is critical to biological activity, and elimination of the asparagine at position 28 serves to increase the effect that asparagine at position 113 possesses.

[0142] The domains required for G-CSF receptor binding were also determined based on the above analogs prepared and the G-CSF structure. The G-CSF receptor binding domain is located at residues (with methionine being position 1) 11-57 (between the A and AB helix) and 100-118 (between the B and C helices). One may also prepare abbreviated molecules capable of binding to a G-CSF receptor and initiate signal transduction for selectively stimulating neutrophils by changing the external loop structure and having the receptor binding domains remain intact.

[0143] Residues essential for biological activity and presumably G-CSF receptor binding or signal transduction have been identified. Two distinct sites are located on two different regions of the secondary structure. What is here called "Site A" is located on a helix which is constrained by salt bridge contacts between two other members of the helical bundle. The second site, "Site B" is located on a relatively more flexible helix, AB. The AB helix is potentially more sensitive to local pH changes because of the type and position of the residues at the carboxy and amino termini. The functional importance of this flexible helix may be important in a conformationally induced fit when binding to the G-CSF receptor. Additionally, the extended portion of the D helix is also indicated to be a G-CSF receptor binding domain, as

ascertained by direct mutational and indirect comparative protein structure analysis. Deletion of the carboxy terminal end of r-hu-met-G-CSF reduces activity as it does for hGH, *see* Cunningham and Wells, *Science* **244**: 1081-1084 (1989). Cytokines which have similar structures, such as IL-6 and GM-CSF with predicted similar topology also center their biological activity along the carboxy end of the D helix, *see* Bazan, *Immunology Today* **11**: 350-354 (1990)

[0144] A comparison of the structures and the positions of G-CSF receptor binding determinants between G-CSF and hGH suggests both molecules have similar means of signal transduction. Two separate G-CSF receptor binding sites have been identified for hGH De Vos et al., *Science* **255**: 306-32 (1991). One of these binding sites (called "Site I") is formed by residues on the exposed faces of hGH's helix 1, the connection region between helix 1 and 2, and helix 4. The second binding site (called "Site II") is formed by surface residues of helix 1 and helix 3.

[0145] The G-CSF receptor binding determinates identified for G-CSF are located in the same relative positions as those identified for hGH. The G-CSF receptor binding site located in the connecting region between helix A and B on the AB helix (Site A) is similar in position to that reported for a small piece of helix (residues 38-47) of hGH. A single point mutation in the AB helix of G-CSF significantly reduces biological activity (as ascertained in the present assays), indicating the role in a G-CSF receptor-ligand interface. Binding of the G-CSF receptor may destabilize the 3¹⁰ helical nature of this region and induce a conformation change improving the binding energy of the ligand/G-CSF receptor complex.

[0146] In the hGH receptor complex, the first helix of the bundle donates residues to both of the binding sites required to dimerize the hGH receptor. Mutational analysis of the corresponding helix of G-CSF (helix A) has identified three residues which are required for biological activity. Of these three residues, Glu 20 and Arg 24 lie on one face of the helical bundle towards helix C, whereas the side chain of Arg 23 (in two of the three molecules in the asymmetric unit) points to the face of the bundle towards helix D. The position of side chains of these biologically important residues indicates that similar to hGH, G-CSF may have a second G-CSF receptor binding site along the interface between helix A and helix C. In contrast with the hGH molecule, the amino terminus of G-CSF has a limited biological role as deletion of the first 11 residues has little effect on the biological activity.

[0147] As indicated above (*see* FIGURE 2, for example), G-CSF has a topological similarity with other cytokines. A correlation of the structure with previous biochemical studies, mutational analysis and direct comparison of specific residues of the hGH receptor complex indicates that G-CSF has two receptor binding sites. Site A lies along the interface of the A and D helices and includes residues in the small AB helix. Site B also includes residues in the A helix but lies along the interface between helices A and C. The conservation of structure and relative positions of biologically important residues between G-CSF and hGH is one indication of a common method of signal transduction in that the receptor is bound in two places. It is therefore found that G-CSF analogs possessing altered G-CSF receptor binding domains may be prepared by alteration at either of the G-CSF receptor binding sites (residues 20-57 and 145-175).

[0148] Knowledge of the three dimensional structure and correlation of the composition of G-CSF protein makes possible a systematic, rational method for preparing G-CSF analogs. The above working examples have demonstrated that the limitations of the size and polarity of the side chains within the core of the structure dictate how much change the molecule can tolerate before the overall structure is changed.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Amgen Inc.

(ii) TITLE OF INVENTION: G-CSF ANALOG COMPOSITIONS AND METHODS

(iii) NUMBER OF SEQUENCES: 110

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Amgen Inc.
(B) STREET: Amgen Center, 1840 DeHavilland Drive
(C) CITY: Thousand Oaks
(D) STATE: California
(E) COUNTRY: United States of America
(F) ZIP: 91320-1789

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 565 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 30..554

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TCTAGAAAAA	ACCAAGGAGG	TAATAAATA	ATG	ACT	CCA	TTA	GGT	CCT	GCT	TCT	53					
			Met	Thr	Pro	Leu	Gly	Pro	Ala	Ser						
			1				5									
TCT	CTG	CCG	CAA	AGC	TTT	CTG	CTG	AAA	TGT	CTG	GAA	CAG	GTT	CGT	AAA	101
Ser	Leu	Pro	Gln	Ser	Phe	Leu	Leu	Lys	Cys	Leu	Glu	Gln	Val	Arg	Lys	
	10					15					20					
ATC	CAG	GGT	GAC	GGT	GCT	GCA	CTG	CAA	GAA	AAA	CTG	TGC	GCT	ACT	TAC	149
Ile	Gln	Gly	Asp	Gly	Ala	Ala	Leu	Gln	Glu	Lys	Leu	Cys	Ala	Thr	Tyr	
	25				30					35					40	

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5 AAA CTG TGC CAT CCG GAA GAG CTG GTA CTG CTG GGT CAT TCT CTT GGG 197
 Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly
 45 50 55

10 ATC CCG TGG GCT CCG CTG TCT TCT TGT CCA TCT CAA GCT CTT CAG CTG 245
 Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu
 60 65 70

15 GCT GGT TGT CTG TCT CAA CTG CAT TCT GGT CTG TTC CTG TAT CAG GGT 293
 Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
 75 80 85

20 CTT CTG CAA GCT CTG GAA GGT ATC TCT CCG GAA CTG GGT CCG ACT CTG 341
 Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu
 90 95 100

25 GAC ACT CTG CAG CTA GAT GTA GCT GAC TTT GCT ACT ACT ATT TGG CAA 389
 Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln
 105 110 115 120

30 CAG ATG GAA GAG CTC GGT ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT 437
 Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly
 125 130 135

35 GCT ATG CCG GCA TTC GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA 485
 Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val
 140 145 150

40 CTG GTT GCT TCT CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT 533
 Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val
 155 160 165

45 CTG CGT CAT CTG GCT CAG CCG TAATAGAATT C 565
 Leu Arg His Leu Ala Gln Pro
 170 175

(c) INFORMATION FOR SEQ ID NO:2:

35 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 175 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

40 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45

50

55

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Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
5 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
10 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
15 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
20 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:3:

25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATTCTGCTG CGTTGTCTGG AACA

24

35 (2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
40 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

45 ACAGGTTCGT CGTATCCAGG GTG

23

50

55

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CACTGCAAGA ACGTCTGTGC GCT

23

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CGCTACTTAC CGTCTGTGCC ATC

23

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTTTCTGCTG CGTTGTCTGG AACAA

24

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

ACAGGTTTCGT CGTATCCAGG GTG

23

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CTGCAAGA ACGTCTGTGC GCT

23

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CITTCCTGCTG CGTTGTCTGG AACAA

24

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ACAGGTTTCGT CGTATCCAGG GTG

23

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CGCTACTTAC CGTCTGTCCC ATC

23

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CTTTCTGCTG CGTTGTCTGG AACA

24

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTGCAAGA ACGTCTGTGC GCT

23

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CGCTACTTAC CGTCTGTGCC ATC

23

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(2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ACAGGTTTCGT CGTATCCAGG GTG

23

(2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CACTGCAAGA ACGTCTGTGC GCT

23

(2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CGCTACTTAC CGTCTGTGCC ATC

23

(2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CTTTCTGCTG CGTTGTCTGG AACA

24

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AGGTTTGGT CGTATCCAGG GTG

23

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CACTGCAAGA ACGTCTGTGC GCT

23

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CGCTACTTAC CGTCTGTGCC ATC

23

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TCTGCTGAAA GCTCTGGAAC AGG

23

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CTTGTCATC TGAAGCTCTT CAG

23

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CTAAACTGT CCGCTACTTA CAACTGTCC CATCOGG

37

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TTCGTAAAAT CGCGGGTGAC GG

22

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

TCATCTGGCT GCGCGTAAT AG

22

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CCGTGTTCTG GTCATCTGG CT

22

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 24 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GAAGTATCTT ACGCTGTTCT GCGT

24

(2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 25 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GAAGTATCTT ACTAAGTTCT GCGTC

25

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CTACTTAC GCACTGTGCC AT

22

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CAAACGTGTC AAGCCGGAAG AG

22

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CATCCGGAAG CACTGGTACT GC

22

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GGAACAGGTT GCTAAAATCC AGG

23

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GAACAGGTTG GTGCGATCCA GGGTG

25

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CAATGTCTG GCACAGGTTG GT

22

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TCCAGGGTGC CGGTGCTGC

19

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(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

AAGAGCTCGG TGAGGCACCA GCT

23

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTCAAGGTGC TGAGCCGGCA TTC

23

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GAGCTCGGTC TGGCACCAGC

20

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TCAAGGTGCT CTGCCGGCAT T

21

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TGCCGCAA GCCTTTCTGC TGA

23

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CTTTCTGCTG GCATGTCTGG AACA

24

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CTATTGGCA AGCGATGGAA GAGC

24

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CAGATGGAAG CGCTCGGTAT G

21

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GAGCTCGGTC TGGCACCAGC

20

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

TAGGTGCT CTGCCGGCAT T

21

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GAAATGTCTG GCACAGGTTT GT

22

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(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TTCCGGAGCG CACAGTTTG

19

(2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CGAGAAGGCC TCGGGTGTCA AAC

23

(2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

ATGCCAAATT GCAGTAGCAA AG

22

(2) INFORMATION FOR SEQ ID NO:52:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ACAACGGTTT AACGTCATCG TTTC

24

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

ATCAGCTACT GCTAGCTGCA GA

22

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

TCAGTCGATG ACGATCGACG TCT

23

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

TTACGAACCG CTTCCAGACA TT

22

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 25 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TAAAATGCTT GGCGAAGGTC TGTA

25

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GTCAGCAATG CAGCTACATC TA

22

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CTCATCGTT TACGTCGATG TAGAT

25

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

CCAAGAGAAG CACCCAGCAG

20

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

AGGGTTCTCT TCGTGGGTCG TC

22

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CACTGGCGGT GATAATGAGC

20

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CTAGGCCAGG CATTACTGG

19

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

5 CCACTGGCGG TGATACTGAG C

21

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

AGCAGAAAGC TTTCCGGCAG AGAAGAAGCA GGA

33

20 (2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

30 GCCGCAAAGC TTTCTGCTGA AATGTCTGGA AGAGGTTCGT AAAATCCAGG GTGA

54

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

- 35 (A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

CTGGAATGCA GAAGCAAATG CCGGCATAGC ACCTTCAGTC GGTTCAGAG CTGGTGCCA

59

45 (2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

- 50 (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

5 Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
10 Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
15 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
20 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
25 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
30 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
35 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
40 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
45 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140
50 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
55 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

50 Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
55 Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

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Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

5 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

10 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

15 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

I Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

20 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

25

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

40 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

45 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

50 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

55

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Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 5 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 10 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
 35 40 45
 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 40 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 45 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 50 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160

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Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 175 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 175 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

5 Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
10 Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
35 40 45
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
15 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
20 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
25 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
30 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

35 (2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

45 Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
50 Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
35 40 45

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Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

5 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

10 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

15 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Ile Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

20 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

35 Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

40 Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

45 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

50 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

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Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 5 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 10 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 175 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
 35 40 45
 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 35 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 40 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 45 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 50 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

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(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5           10           15
Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
15           20           25           30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
           35           40           45
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
20           50           55           60
Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65           70           75           80
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
25           85           90           95
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
30           100          105          110
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
           115          120          125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
35           130          135          140
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145          150          155          160
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
40           165          170          175

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(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

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Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Ser Ala Thr Tyr Lys Leu Ser His Pro Glu Glu Leu
 35 40 45
 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 r Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 Lys Cys Leu Glu Gln Val Arg Lys Ile Ala Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60

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Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 5 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 10 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 15 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Leu Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175
 20

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 35 Cys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 40 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 45 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 50 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 55

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Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 5 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Ala Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 25 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 30 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 35 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 40 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 45 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 50 Phe Leu Glu Val Ser Tyr Arg Val Leu Ala His Leu Ala Gln Pro
 165 170 175

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(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5           10           15
Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
15          20          25          30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
20          35          40          45
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
25          50          55          60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
30          65          70          75          80
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
35          85          90          95
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
40          100         105         110
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
          115         120         125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
45          130         135         140
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
          145         150         155         160
Phe Leu Glu Val Ser Tyr Ala Val Leu Arg His Leu Ala Gln Pro
50          165         170         175

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(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

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Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
5 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
10 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
15 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
Leu Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
20 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140
25 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
Phe Leu Glu Val Ser Tyr Val Leu Arg His Leu Ala Gln Pro
165 170 174
30

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
45 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Ala Leu Cys His Pro Glu Glu Leu
35 40 45
50 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

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Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Leu Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 175 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

Asn Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Lys Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

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Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 175 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Ala Leu
 35 40 45
 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

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(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 175 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

```

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5           10           15
Lys Cys Leu Glu Gln Val Ala Lys Ile Gln Gly Asp Gly Ala Ala Leu
15          20          25          30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
20          35          40          45
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
25          50          55          60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
30          65          70          75          80
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
35          85          90          95
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
40          100         105         110
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
45          115         120         125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
50          130         135         140
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
55          145         150         155         160
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
60          165         170         175

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(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 175 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

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Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 5 Lys Cys Leu Glu Gln Val Arg Ala Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 10 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 15 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Asp Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 20 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 25 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175
 30

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 175 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 45 Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 50 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60

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Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

5 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

10 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

15 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

16 Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

16 Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

46 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

45 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

50 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

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Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 175 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Glu Ala
 115 120 125
 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

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(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Glu Pro Ala Phe Ala Ser Ala
130 135 140
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

EP 0 612 846 B1

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
5 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
10 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
15 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
S : Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
20 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
115 120 125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140
25 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175
30

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
45 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
50 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

EP 0 612 846 B1

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
5 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
10 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
130 135 140
15 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
Leu Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175
20

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
35 As Ala Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
40 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
45 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
50 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
55

EP 0 612 846 B1

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 5 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
 1 5 10 15
 25 Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 45 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 50 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

EP 0 612 846 B1

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
1 5 10 15
Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

EP 0 612 846 B1

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Gly Phe Leu Leu
 1 5 10 15
 5 Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 10 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 15 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 20 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 25 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 30 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:98:

- 35 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 175 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear
 40 (ii) MOLECULE TYPE: protein
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 45 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 50 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 55

EP 0 612 846 B1

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

5 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

10 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
115 120 125

15 Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

20 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

1 Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ala Phe Leu Leu
5 10 15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

40 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

45 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

50 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

EP 0 612 846 B1

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

Ala Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

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(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

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Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1           5           10           15
Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20           25           30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35           40           45
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50           55           60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65           70           75           80
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85           90           95
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100           105           110
Asp Phe Ala Thr Thr Ile Trp Gln Ala Met Glu Glu Leu Gly Met Ala
115           120           125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130           135           140
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145           150           155           160
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165           170           175

```

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

EP 0 612 846 B1

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
5 Lys Cys Leu Glu Ala Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
10 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
15 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
Leu Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
20 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140
25 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175
30

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
45 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Ala Pro Glu Glu Leu
35 40 45
50 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

EP 0 612 846 B1

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

5 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

10 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

15 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Leu Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

20

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

35 Cys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

40 Val Leu Leu Gly Ala Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

45 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

50 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

55

EP 0 612 846 B1

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

EP 0 612 846 B1

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
Ala Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140
Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

EP 0 612 846 B1

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
5 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
10 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80
15 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95
Leu Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110
20 Asp Phe Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140
25 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175
30

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15
45 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
20 25 30
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45
50 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

EP 0 612 846 B1

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

5 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
100 105 110

10 Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

15 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

20 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

25 Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

40 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

45 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

50 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

EP 0 612 846 B1

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Ala Leu Gly Met Ala
 115 120 125
 5 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 10 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 175 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1 5 10 15
 25 Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
 20 25 30
 30 Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
 35 40 45
 Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
 50 55 60
 35 Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65 70 75 80
 Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
 85 90 95
 40 Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
 100 105 110
 Asp Val Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
 115 120 125
 45 Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
 130 135 140
 Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
 145 150 155 160
 50 Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
 165 170 175

Claims

1. A method for preparing a G-CSF analog comprising the steps of:

- (a) viewing at the amino acid or atomic level information conveying the three dimensional structure of a G-CSF molecule as set forth in Figure 5;
- (b) selecting from said viewed information at least one site on said G-CSF molecule for alteration;
- (c) preparing a G-CSF molecule having such alteration; and
- (d) optionally, testing such G-CSF molecule for a desired characteristic.

2. A method for preparing a G-CSF analog according to claim 1 based on the use of a computer comprising the steps of:

- (a) providing computer expression at the amino acid or atomic level of the three dimensional structure of a G-CSF molecule as set forth in Figure 5;
- (b) selecting from said computer expression at least one site on said G-CSF molecule for alteration;
- (c) preparing a G-CSF molecule having such alteration; and,
- (d) optionally, testing such G-CSF molecule for a desired characteristic.

3. A method for preparing a G-CSF analog according to claim 2 comprising:

- (a) providing said computer with the means for displaying the three dimensional structure of a G-CSF molecule as set forth in Figure 5; including displaying the composition of moieties of said G-CSF molecule, preferably displaying the three dimensional location of each amino acid, and more preferably displaying the three dimensional location of each atom of a G-CSF molecule;
- (b) viewing said display;
- (c) selecting a site on said display for alteration in the composition of said molecule or the location of a moiety; and
- (d) preparing a G-CSF analog with such alteration.

4. A computer-based method for preparing a G-CSF analog comprising the steps of:

- (a) viewing at the amino acid or atomic level the three dimensional structure of a G-CSF molecule as set forth in Figure 5; via a computer, said computer having been previously programmed (i) to express the coordinates of a G-CSF molecule in three dimensional space, and (ii) to allow for entry of information for alteration of said G-CSF expression and viewing thereof;
- (b) selecting a site on said visual image of said G-CSF molecule for alteration;
- (c) entering information for said alteration on said computer;
- (d) viewing a three dimensional structure of said altered G-CSF molecule via said computer;
- (e) optionally repeating steps (a)-(d) above;
- (f) preparing a G-CSF analog with said alteration; and
- (g) optionally testing said G-CSF analog for a desired characteristic.

Patentansprüche

1. Verfahren zur Herstellung eines G-CSF-Analogs, welches die Schritte umfaßt:

- (a) Betrachten, auf dem Aminosäure- oder Atomniveau, von Information, welche die dreidimensionale Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5, vermittelt;
- (b) Auswählen, aus besagter betrachteten Information, von wenigstens einer Stelle auf besagtem G-CSF-Molekül für eine Veränderung;
- (c) Herstellen eines G-CSF-Moleküls mit einer solchen Veränderung; und
- (d) fakultativ, Testen eines solchen G-CSF-Moleküls auf eine gewünschte Eigenschaft.

2. Verfahren zur Herstellung eines G-CSF-Analogs nach Anspruch 1, auf der Basis der Verwendung eines Compu-

ters, welches die Schritte umfaßt:

(a) Bereitstellen einer Computerdarstellung, auf dem Aminosäure- oder Atomniveau, der dreidimensionalen Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5;

(b) Auswählen, aus besagter Computerdarstellung, von wenigstens einer Stelle auf besagtem G-CSF-Molekül für eine Veränderung;

(c) Herstellen eines G-CSF-Moleküls mit einer solchen Veränderung; und

(d) fakultativ, Testen eines solchen G-CSF-Moleküls auf eine gewünschte Eigenschaft.

3. Verfahren zur Herstellung eines G-CSF-Analogs nach Anspruch 2, welches umfaßt:

(a) Versehen besagten Computers mit Mitteln zum Anzeigen der dreidimensionalen Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5, einschließlich Anzeigen der Zusammensetzung der Einheiten besagten G-CSF-Moleküls, vorzugsweise Anzeigen der dreidimensionalen Anordnung jeder Aminosäure und bevorzugter Anzeigen der dreidimensionalen Anordnung jedes Atoms eines G-CSF-Moleküls;

(b) Betrachten besagter Ansicht;

(c) Auswählen einer Stelle auf besagter Ansicht für eine Veränderung in der Zusammensetzung besagten Moleküls oder der Anordnung einer Einheit; und

(d) Herstellen eines G-CSF-Analogs mit solch einer Änderung.

4. Computergestütztes Verfahren zur Herstellung eines G-CSF-Analogs, welches die Schritte umfaßt:

(a) Betrachten, auf dem Aminosäure- oder Atomniveau, der dreidimensionalen Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5, über einen Computer, wobei besagter Computer zuvor so programmiert worden ist, daß er (i) die Koordinaten eines G-CSF-Moleküls im dreidimensionalen Raum darstellt und (ii) die Eingabe von Information zur Veränderung besagter G-CSF-Darstellung und Betrachtung derselben ermöglicht;

(b) Auswählen einer Stelle auf besagtem visuellen Bild besagten G-CSF-Moleküls für eine Veränderung;

(c) Eingeben der Information für besagte Veränderung in besagten Computer;

(d) Betrachten einer dreidimensionalen Struktur besagten veränderten G-CSF-Moleküls über besagten Computer;

(e) fakultativ, Wiederholen der Schritte (a) - (d) oben;

(f) Herstellen eines G-CSF-Analogs mit besagter Veränderung; und

(g) fakultativ, Testen besagten G-CSF-Analogs auf eine gewünschte Eigenschaft.

Revendications

1. Procédé pour préparer un analogue de G-CSF, comprenant les étapes de :

(a) visualiser au niveau atomique ou des acides aminés des informations fournissant la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5,

(b) choisir à partir desdites informations visualisées au moins un site sur ladite molécule de G-CSF pour altération ;

(c) préparer une molécule de G-CSF ayant une telle altération ; et

(d) éventuellement, tester une telle molécule de G-CSF en ce qui concerne une caractéristique souhaitée.

2. Procédé pour préparer un analogue de G-CSF selon la revendication 1, basé sur l'utilisation d'un ordinateur, com-

prenant les étapes de :

- (a) fournir l'expression par ordinateur au niveau atomique ou des acides aminés de la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5,
- (b) choisir à partir de ladite expression par ordinateur au moins un site sur ladite molécule de G-CSF pour altération ;
- (c) préparer une molécule de G-CSF ayant une telle altération ; et
- (d) éventuellement, tester une telle molécule de G-CSF en ce qui concerne une caractéristique souhaitée.

3. Procédé pour préparer un analogue de G-CSF selon la revendication 2, comprenant :

- (a) munir ledit ordinateur des moyens pour afficher la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5 incluant l'affichage de la composition des fractions de ladite molécule de G-CSF, en affichant de préférence l'emplacement tridimensionnel de chaque acide aminé, et, plus préférentiellement, en affichant l'emplacement tridimensionnel de chaque atome d'une molécule de G-CSF ;
- (b) visualiser ledit affichage ;
- (c) choisir un site sur ledit affichage pour altération de la composition de ladite molécule ou de l'emplacement d'une fraction ; et
- (d) préparer un analogue de G-CSF ayant une telle altération.

4. Procédé assisté par ordinateur pour préparer un analogue de G-CSF, comprenant les étapes de :

- (a) visualiser au niveau atomique ou des acides aminés la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5 via un ordinateur, ledit ordinateur ayant été préalablement programmé (i) pour exprimer les coordonnées d'une molécule de G-CSF dans l'espace tridimensionnel, et (ii) pour permettre l'entrée des informations pour l'altération de ladite expression de G-CSF et sa visualisation ;
- (b) choisir un site sur ladite image visuelle de ladite molécule de G-CSF pour altération ;
- (c) entrer des informations pour ladite altération dans ledit ordinateur ;
- (d) visualiser une structure tridimensionnelle de ladite molécule de G-CSF altérée via ledit ordinateur ;
- (e) répéter éventuellement les étapes (a) - (d) ci-dessus ;
- (f) préparer un analogue de G-CSF ayant ladite altération ; et
- (g) tester éventuellement ledit analogue de G-CSF en ce qui concerne une caractéristique souhaitée.

EP 0 612 846 B1

Met Thr Pro Leu Gly Pro Ala
TCTAGAAAAACCAAGTAGGTAATAATA ATG ACT CCA TTA GGT CCT CCT

Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Gly Gln
TCT TCT CTG CCG CAA AGC TTT CTG CTG AAA TGT CTG GAA CAG

Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu
GTT CGT AAA ATC CAG GGT GAC GGT GCT GCA CTG CAA GAA AAA CTG

Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu
TGC GCT ACT TAC AAA CTG TGC CAT CCG GAA GAG CTG GTA CTG CTG

Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro
GGT CAT TCT CTT GGG ATC CCG TGG GCT CCG CTG TCT TCT TGT CCA

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser
TCT CAA GCT CTT CAG CTG GCT GGT TGT CTG TCT CAA CTG CAT TCT

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
GGT CTG TTC CTG TAT CAG GGT CTT CTG CAA GCT CTG GAA GGT ATC

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val
TCT CCG GAA CTG GGT CCG ACT CTG GAC ACT CTG CAG CTA GAT GTA

Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly
GCT GAC TTT GCT ACT ACT ATT TGG CAA CAG ATG GAA GAG CTC GGT

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT GCT ATG CCG GCA TTC

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA CTG GTT GCT TCT

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT CTG CGT CAT

Leu Ala Gln Pro OC AM
CTG GCT CAG CCG TAA TAG AATTC

FIGURE 1

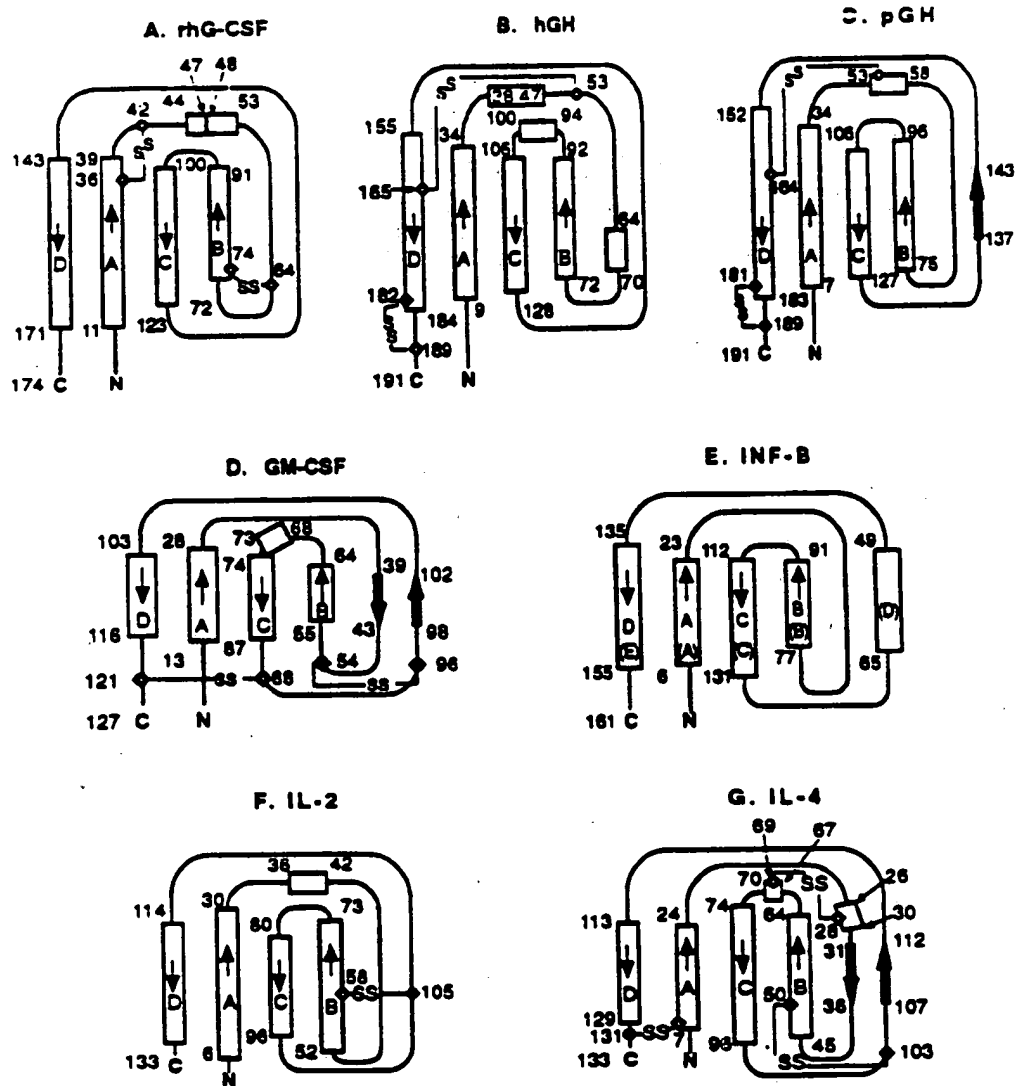


FIGURE 2

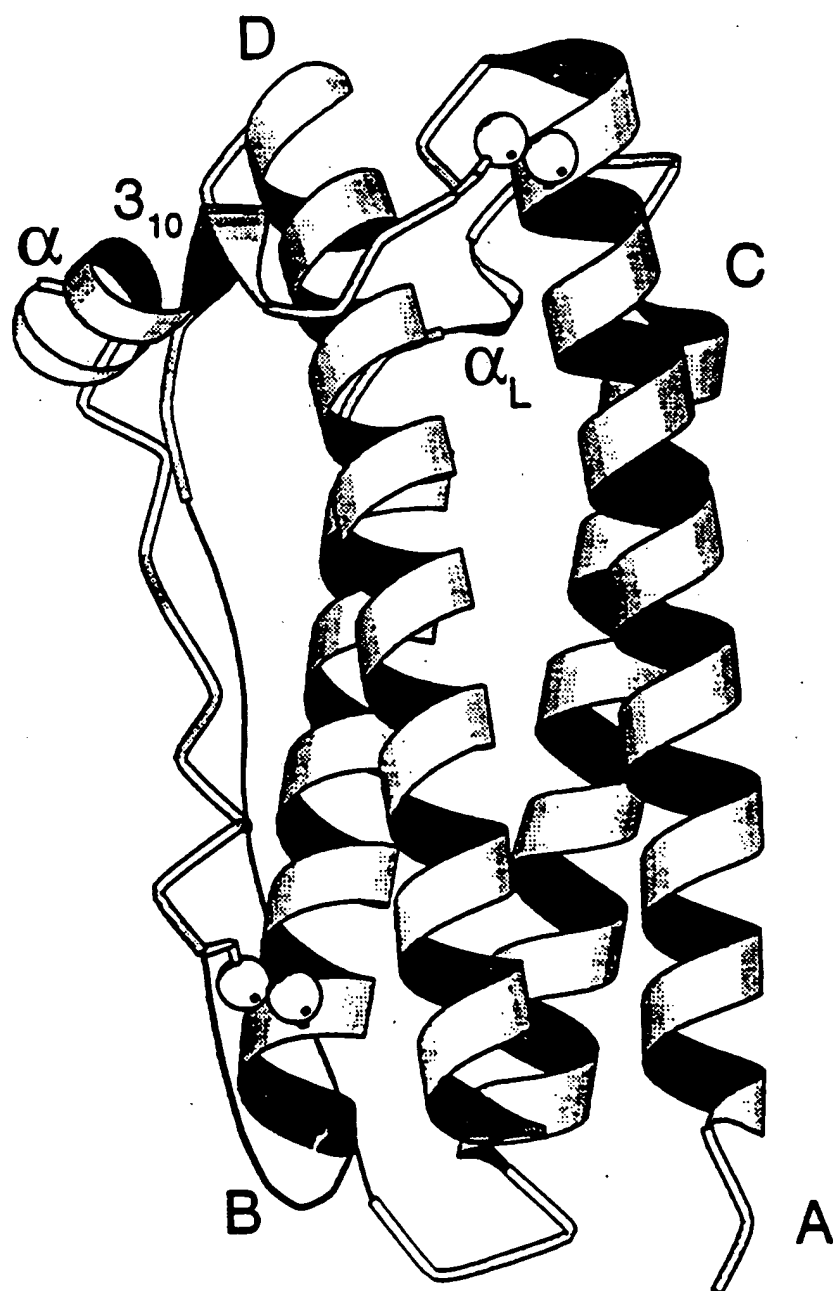


FIGURE 3

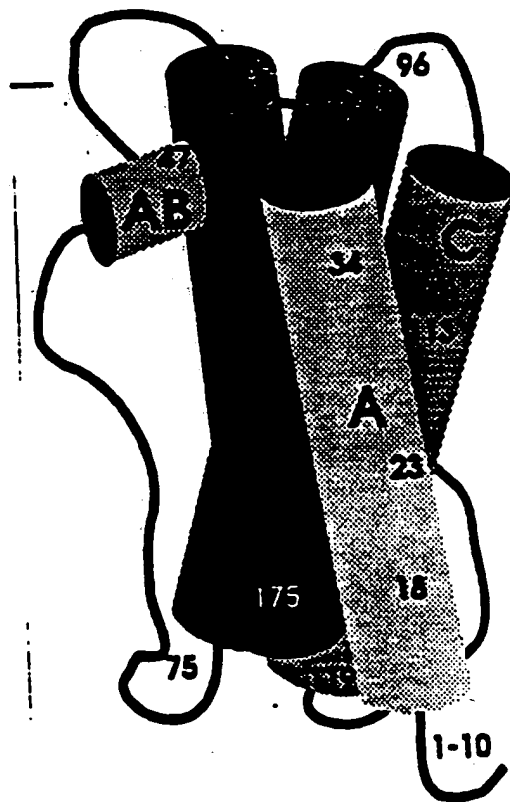


FIGURE 4

FIGURE 5

ATOM	1	CB	LEU	10	58.751	58.191	-14.868	1.00	61.22	AI
ATOM	2	CG	LEU	10	58.360	59.271	-13.939	1.00	60.19	AI
ATOM	3	CN	LEU	10	59.307	60.461	-14.022	1.00	60.14	AI
ATOM	4	CD2	LEU	10	56.954	59.658	-14.335	1.00	60.68	AI
ATOM	5	C	LEU	10	60.344	56.734	-13.849	1.00	62.85	AI
ATOM	6	O	LEU	10	60.079	55.595	-14.041	1.00	63.08	AI
ATOM	7	HT1	LEU	10	59.876	56.135	-15.998	1.00	0.00	AI
ATOM	8	HT2	LEU	10	61.323	56.887	-16.434	1.00	0.00	AI
ATOM	9	N	LEU	10	60.328	57.059	-16.204	1.00	62.24	AI
ATOM	10	HT3	LEU	10	59.817	57.535	-16.971	1.00	0.00	AI
ATOM	11	CA	LEU	10	60.183	57.758	-14.941	1.00	62.58	AI
ATOM	12	N	PRO	11	61.357	56.962	-12.780	1.00	61.96	AI
ATOM	13	CD	PRO	11	61.960	58.238	-12.383	1.00	61.21	AI
ATOM	14	CA	PRO	11	61.832	55.889	-11.906	1.00	61.34	AI
ATOM	15	CB	PRO	11	62.915	56.547	-11.043	1.00	59.77	AI
ATOM	16	CG	PRO	11	62.311	57.983	-10.975	1.00	59.16	AI
ATOM	17	C	PRO	11	60.712	55.225	-11.109	1.00	60.68	AI
ATOM	18	O	PRO	11	60.075	55.843	-10.350	1.00	61.73	AI
ATOM	19	N	GLN	12	60.466	53.946	-11.407	1.00	59.31	AI
ATOM	20	H	GLN	12	60.944	53.573	-12.175	1.00	0.00	AI
ATOM	21	CA	GLN	12	59.468	53.121	-10.743	1.00	57.22	AI
ATOM	22	CB	GLN	12	59.779	51.646	-10.970	1.00	59.70	AI
ATOM	23	CG	GLN	12	58.620	50.714	-10.591	1.00	59.70	AI
ATOM	24	C	GLN	12	57.604	50.575	-11.702	1.00	61.71	AI
ATOM	25	O	GLN	12	57.170	49.465	-11.970	1.00	65.82	AI
ATOM	26	NE2	GLN	12	57.227	51.534	-12.541	1.00	63.02	AI
ATOM	27	HE2	GLN	12	57.639	52.419	-12.489	1.00	0.00	AI
ATOM	28	HE2	GLN	12	56.500	51.308	-13.156	1.00	0.00	AI
ATOM	29	C	GLN	12	59.336	53.347	-9.245	1.00	55.34	AI
ATOM	30	O	GLN	12	58.242	53.196	-8.708	1.00	54.56	AI
ATOM	31	N	SER	13	60.423	53.732	-8.576	1.00	53.44	AI
ATOM	32	H	SER	13	61.276	53.839	-9.033	1.00	0.00	AI
ATOM	33	CA	SER	13	60.335	53.974	-7.168	1.00	52.86	AI
ATOM	34	CB	SER	13	61.704	54.144	-6.626	1.00	52.24	AI
ATOM	35	CG	SER	13	61.702	53.493	-5.362	1.00	56.64	AI
ATOM	36	HG	SER	13	61.534	52.551	-5.477	1.00	0.00	AI
ATOM	37	C	SER	13	59.497	55.214	-6.900	1.00	52.58	AI
ATOM	38	O	SER	13	58.509	55.144	-6.160	1.00	53.55	AI
ATOM	39	N	PIE	14	59.791	56.333	-7.577	1.00	50.84	AI
ATOM	40	H	PIE	14	60.469	56.292	-8.279	1.00	0.00	AI
ATOM	41	CA	PIE	14	59.067	57.590	-7.423	1.00	47.21	AI
ATOM	42	CB	PIE	14	59.611	58.590	-8.454	1.00	44.68	AI
ATOM	43	CG	PIE	14	58.618	59.669	-8.866	1.00	42.88	AI
ATOM	44	CD1	PIE	14	58.032	59.594	-10.123	1.00	40.40	AI
ATOM	45	CD2	PIE	14	58.264	60.673	-7.978	1.00	40.30	AI
ATOM	46	CE1	PIE	14	57.114	60.518	-10.507	1.00	39.59	AI
ATOM	47	CE2	PIE	14	57.329	61.587	-8.380	1.00	41.82	AI
ATOM	48	CZ	PIE	14	56.751	61.515	-9.635	1.00	41.56	AI
ATOM	49	C	PIE	14	57.605	57.263	-7.661	1.00	45.83	AI
ATOM	50	O	PIE	14	56.789	57.588	-6.805	1.00	46.17	AI
ATOM	51	N	LEU	15	57.298	56.509	-8.718	1.00	44.64	AI
ATOM	52	H	LEU	15	55.024	56.183	-9.287	1.00	0.00	AI
ATOM	53	CA	LEU	15	55.940	56.181	-9.038	1.00	44.53	AI
ATOM	54	CB	LEU	15	55.858	55.402	-10.300	1.00	48.72	AI
ATOM	55	CG	LEU	15	54.853	56.013	-11.269	1.00	51.65	AI
ATOM	56	CD1	LEU	15	55.535	57.121	-12.105	1.00	50.33	AI
ATOM	57	CD2	LEU	15	54.320	54.906	-12.204	1.00	53.77	AI
ATOM	58	C	LEU	15	55.169	55.410	-8.014	1.00	44.07	AI
ATOM	59	O	LEU	15	53.945	55.567	-7.959	1.00	45.46	AI
ATOM	60	N	LEU	16	55.809	54.620	-7.166	1.00	43.18	AI
ATOM	61	H	LEU	16	56.781	54.503	-7.251	1.00	0.00	AI
ATOM	62	CA	LEU	16	55.110	53.913	-6.095	1.00	42.96	AI
ATOM	63	CB	LEU	16	55.866	52.623	-5.751	1.00	43.14	AI
ATOM	64	CG	LEU	16	55.840	51.608	-6.868	1.00	42.25	AI
ATOM	65	CD1	LEU	16	56.889	50.567	-6.596	1.00	41.68	AI
ATOM	66	CD2	LEU	16	54.413	51.068	-7.030	1.00	42.75	AI
ATOM	67	C	LEU	16	54.963	54.778	-4.852	1.00	42.35	AI
ATOM	68	O	LEU	16	54.077	54.579	-4.018	1.00	42.65	AI
ATOM	69	N	LYS	17	55.821	55.779	-4.703	1.00	42.47	AI
ATOM	70	H	LYS	17	56.587	55.840	-5.320	1.00	0.00	AI
ATOM	71	CA	LYS	17	55.681	56.767	-3.650	1.00	42.07	AI
ATOM	72	CB	LYS	17	56.955	57.554	-3.573	1.00	44.14	AI
ATOM	73	CG	LYS	17	57.214	58.197	-2.223	1.00	49.61	AI
ATOM	74	CD	LYS	17	57.114	57.164	-1.086	1.00	55.15	AI
ATOM	75	CE	LYS	17	56.747	57.804	0.293	1.00	62.05	AI
ATOM	76	N2	LYS	17	55.462	58.533	0.331	1.00	65.43	AI
ATOM	77	HE2	LYS	17	54.684	57.884	0.098	1.00	0.00	AI
ATOM	78	HE2	LYS	17	55.482	59.308	-0.362	1.00	0.00	AI
ATOM	79	HE2	LYS	17	55.312	58.926	1.282	1.00	0.00	AI
ATOM	80	C	LYS	17	54.463	57.640	-4.051	1.00	41.20	AI
ATOM	81	O	LYS	17	53.648	57.999	-3.186	1.00	40.66	AI
ATOM	82	N	CYS	18	54.272	57.992	-5.346	1.00	39.13	AI
ATOM	83	H	CYS	18	54.298	57.809	-5.981	1.00	0.00	AI
ATOM	84	CA	CYS	18	53.050	58.656	-5.802	1.00	37.42	AI
ATOM	85	CB	CYS	18	53.092	58.891	-7.261	1.00	35.02	AI
ATOM	86	SC	CYS	18	54.421	60.076	-7.681	1.00	40.40	AI
ATOM	87	C	CYS	18	51.859	57.789	-5.502	1.00	39.33	AI
ATOM	88	O	CYS	18	50.959	58.346	-4.847	1.00	40.83	AI
ATOM	89	N	LEU	19	51.738	56.475	-5.842	1.00	37.15	AI
ATOM	90	H	LEU	19	52.462	56.038	-6.341	1.00	0.00	AI
ATOM	91	CA	LEU	19	50.521	55.702	-5.534	1.00	36.00	AI
ATOM	92	CB	LEU	19	50.644	54.204	-5.947	1.00	38.31	AI
ATOM	93	CG	LEU	19	49.410	53.271	-5.657	1.00	40.80	AI
ATOM	94	CD1	LEU	19	48.208	53.684	-6.467	1.00	39.71	AI
ATOM	95	CD2	LEU	19	49.692	51.833	-6.113	1.00	45.71	AI
ATOM	96	C	LEU	19	50.102	55.736	-4.076	1.00	31.52	AI
ATOM	97	O	LEU	19	48.930	55.949	-3.766	1.00	32.25	AI
ATOM	98	N	GLU	20	51.030	55.576	-3.166	1.00	41.88	AI
ATOM	99	H	GLU	20	51.940	55.338	-3.455	1.00	0.00	AI
ATOM	100	CA	GLU	20	50.750	55.710	-1.748	1.00	31.40	AI

FIGURE 5

ATOM	101	CB	GLU	20	52.053	55.334	-1.167	1.00	35.25	AI	152	NZ	LVS	24	51.532	59.975	3.333	1.00	51.19	AI
ATOM	102	CG	GLU	20	52.508	55.504	0.260	1.00	43.21	AI	153	IZ1	LVS	24	51.637	60.498	4.225	1.00	0.00	AI
ATOM	103	OD	GLU	20	53.948	54.947	0.407	1.00	51.06	AI	154	IZ2	LVS	24	51.539	60.651	2.539	1.00	0.00	AI
ATOM	104	CI	GLU	20	54.320	54.660	1.546	1.00	56.78	AI	155	IZ3	LVS	24	52.317	59.303	3.216	1.00	0.00	AI
ATOM	105	OE2	GLU	20	54.708	54.766	-0.570	1.00	51.57	AI	156	C	LVS	24	45.455	59.893	1.101	1.00	21.66	AI
ATOM	106	C	GLU	20	50.230	57.117	-1.326	1.00	33.25	AI	157	O	LVS	24	44.588	60.068	1.962	1.00	20.78	AI
ATOM	107	O	GLU	20	49.432	57.291	-0.380	1.00	33.30	AI	158	N	LVS	24	45.549	60.696	0.044	1.00	21.46	AI
ATOM	108	H	GLN	21	50.660	58.167	-2.044	1.00	32.33	AI	159	II	LVS	25	46.242	60.509	-0.629	1.00	0.00	AI
ATOM	109	H	GLN	21	51.270	58.004	-2.794	1.00	0.00	AI	160	CA	LVS	25	44.667	61.841	-0.115	1.00	22.53	AI
ATOM	110	CA	GLN	21	50.275	59.538	-1.742	1.00	31.00	AI	161	CB	LVS	25	45.075	62.694	-1.307	1.00	22.15	AI
ATOM	111	CB	GLN	21	51.376	60.489	-2.340	1.00	32.37	AI	162	CG2	LVS	25	44.097	63.834	-1.439	1.00	20.44	AI
ATOM	112	CG	GLN	21	52.436	60.530	-1.272	1.00	38.01	AI	163	CD	LVS	25	46.475	63.230	-1.136	1.00	21.03	AI
ATOM	113	OD	GLN	21	53.622	61.460	-1.504	1.00	42.67	AI	164	CG1	LVS	25	47.188	63.281	-2.497	1.00	20.04	AI
ATOM	114	CI	GLN	21	54.008	62.736	-0.615	1.00	43.63	AI	165	C	LVS	25	43.263	61.308	-0.352	1.00	21.75	AI
ATOM	115	NE2	GLN	21	54.256	61.448	-2.678	1.00	42.31	AI	166	O	LVS	25	42.339	61.839	0.301	1.00	26.13	AI
ATOM	116	HE21	GLN	21	53.965	60.840	-3.364	1.00	0.00	AI	167	N	GLN	26	43.065	60.289	-1.244	1.00	22.79	AI
ATOM	117	HE22	GLN	21	55.026	62.052	-2.730	1.00	0.00	AI	168	II	GLN	26	43.842	59.926	-1.726	1.00	0.00	AI
ATOM	118	C	GLN	21	48.094	59.765	-2.288	1.00	28.51	AI	169	CA	GLN	26	41.737	59.713	-1.437	1.00	20.12	AI
ATOM	119	O	GLN	21	48.027	60.242	-1.563	1.00	28.65	AI	170	CB	GLN	26	41.729	58.539	-2.341	1.00	18.89	AI
ATOM	120	N	VAL	22	48.682	59.319	-3.521	1.00	25.85	AI	171	CG	GLN	26	42.203	59.042	-3.627	1.00	19.77	AI
ATOM	121	H	VAL	22	49.448	58.980	-4.013	1.00	0.00	AI	172	CD	GLN	26	42.163	57.996	-4.684	1.00	24.26	AI
ATOM	122	CA	VAL	22	47.382	59.303	-4.161	1.00	24.94	AI	173	OE1	GLN	26	42.550	56.853	-4.465	1.00	25.82	AI
ATOM	123	CB	VAL	22	47.508	58.614	-5.526	1.00	24.09	AI	174	NE2	GLN	26	41.732	58.351	-5.890	1.00	27.68	AI
ATOM	124	CG1	VAL	22	46.154	58.378	-6.096	1.00	19.97	AI	175	HE21	GLN	26	41.421	59.265	-6.042	1.00	0.00	AI
ATOM	125	CG2	VAL	22	48.252	59.479	-6.498	1.00	25.82	AI	176	HE22	GLN	26	41.743	57.649	-6.552	1.00	0.00	AI
ATOM	126	C	VAL	22	46.418	58.549	-3.226	1.00	25.65	AI	177	C	GLN	26	41.207	59.239	-0.111	1.00	21.88	AI
ATOM	127	O	VAL	22	45.428	59.190	-2.800	1.00	29.31	AI	178	O	GLN	26	40.067	59.550	0.220	1.00	27.02	AI
ATOM	128	N	ARG	23	46.643	57.291	-2.759	1.00	23.93	AI	179	N	GLY	27	41.952	58.622	0.773	1.00	22.54	AI
ATOM	129	H	ARG	23	47.440	56.819	-3.056	1.00	0.00	AI	180	II	GLY	27	42.891	58.420	0.375	1.00	0.00	AI
ATOM	130	CA	ARG	23	45.667	56.593	-1.892	1.00	20.67	AI	181	CA	GLY	27	40.936	59.352	2.890	1.00	27.80	AI
ATOM	131	CB	ARG	23	46.104	55.135	-1.635	1.00	20.45	AI	182	C	GLY	27	39.889	59.231	3.526	1.00	29.95	AI
ATOM	132	CG	ARG	23	46.325	54.321	-2.904	1.00	17.51	AI	183	O	GLY	27	41.683	60.460	2.915	1.00	29.37	AI
ATOM	133	CD	ARG	23	45.095	54.446	-3.769	1.00	21.54	AI	184	N	ASP	28	42.547	60.454	2.448	1.00	0.00	AI
ATOM	134	NE	ARG	23	45.076	53.437	-4.809	1.00	24.82	AI	185	H	ASP	28	41.237	61.680	3.624	1.00	28.35	AI
ATOM	135	HE	ARG	23	45.642	52.647	-4.701	1.00	0.00	AI	186	CA	ASP	28	42.266	62.789	3.552	1.00	30.13	AI
ATOM	136	CZ	ARG	23	44.373	53.556	-5.904	1.00	27.69	AI	187	CB	ASP	28	42.266	62.789	3.552	1.00	30.13	AI
ATOM	137	NH1	ARG	23	43.567	54.669	-6.006	1.00	29.51	AI	188	CG	ASP	28	43.737	62.502	3.777	1.00	31.72	AI
ATOM	138	NH11	ARG	23	43.562	55.377	-5.303	1.00	0.00	AI	189	OD1	ASP	28	44.539	63.074	2.995	1.00	31.95	AI
ATOM	139	NH12	ARG	23	42.956	54.730	-6.789	1.00	0.00	AI	190	OD2	ASP	28	44.063	61.811	-4.741	1.00	32.00	AI
ATOM	140	NH2	ARG	23	43.780	52.713	-7.709	1.00	0.00	AI	191	C	ASP	28	39.994	62.264	2.960	1.00	25.81	AI
ATOM	141	NH21	ARG	23	44.936	51.802	-6.793	1.00	0.00	AI	192	O	ASP	28	39.101	62.699	3.655	1.00	26.21	AI
ATOM	142	NH22	ARG	23	44.345	52.604	-6.891	1.00	24.22	AI	193	N	GLY	29	39.882	62.270	1.631	1.00	23.93	AI
ATOM	143	C	ARG	23	45.458	57.285	-0.560	1.00	20.56	AI	194	H	GLY	29	40.660	61.950	1.135	1.00	31.00	AI
ATOM	144	O	ARG	23	44.374	57.254	-0.042	1.00	20.04	AI	195	CA	GLY	29	38.779	62.694	0.886	1.00	25.69	AI
ATOM	145	N	LVS	24	46.485	58.015	-0.118	1.00	22.67	AI	196	C	GLY	29	37.328	61.961	1.418	1.00	27.36	AI
ATOM	146	II	LVS	24	47.291	58.105	-0.668	1.00	0.00	AI	197	O	GLY	29	36.648	62.558	2.061	1.00	28.14	AI
ATOM	147	CA	LVS	24	46.431	58.729	1.166	1.00	22.85	AI	198	N	ALA	30	37.646	60.628	1.295	1.00	27.85	AI
ATOM	148	CB	LVS	24	47.811	59.255	1.506	1.00	26.86	AI	199	II	ALA	30	38.442	60.288	0.843	1.00	0.00	AI
ATOM	149	CG	LVS	24	47.821	59.661	2.971	1.00	33.79	AI	200	CA	ALA	30	36.683	59.655	1.814	1.00	25.94	AI
ATOM	150	CD	LVS	24	49.121	60.265	3.404	1.00	40.73	AI	201	CB	ALA	30	37.269	58.303	1.556	1.00	22.15	AI
ATOM	151	CE	LVS	24	50.258	59.258	3.335	1.00	46.19	AI	202	C	ALA	30	36.356	59.842	3.308	1.00	27.18	AI

FIGURE 5

ATOM	203	O	ALA	30	35.194	59.772	3.754	1.00	28.82	AI	ATOM	254	N	LEU	36	30.652	64.190	6.480	1.00	41.21	AI
ATOM	204	N	ALA	31	37.340	60.105	4.150	1.00	27.16	AI	ATOM	255	II	LEU	36	31.343	63.930	5.836	1.00	40.00	AI
ATOM	205	II	ALA	31	38.253	60.114	3.809	1.00	0.00	AI	ATOM	256	CA	LEU	36	29.647	65.157	6.144	1.00	40.25	AI
ATOM	206	CA	ALA	31	37.113	60.470	5.531	1.00	27.70	AI	ATOM	257	CB	LEU	36	30.070	65.899	4.889	1.00	39.03	AI
ATOM	207	CB	ALA	31	38.383	60.881	6.177	1.00	27.65	AI	ATOM	258	CG	LEU	36	31.753	66.834	4.935	1.00	33.99	AI
ATOM	208	C	ALA	31	36.178	61.675	5.660	1.00	30.01	AI	ATOM	259	CD1	LEU	36	31.438	67.404	3.571	1.00	32.08	AI
ATOM	209	O	ALA	31	35.195	61.624	6.413	1.00	32.91	AI	ATOM	260	CD2	LEU	36	31.034	67.939	5.928	1.00	35.05	AI
ATOM	210	N	LEU	32	36.397	62.744	4.895	1.00	27.63	AI	ATOM	261	C	LEU	36	28.332	64.414	5.941	1.00	41.90	AI
ATOM	211	II	LEU	32	37.133	62.734	4.242	1.00	0.00	AI	ATOM	262	O	LEU	36	27.267	64.828	6.431	1.00	42.30	AI
ATOM	212	CA	LEU	32	35.560	63.898	4.997	1.00	28.52	AI	ATOM	263	N	CYS	37	28.392	63.251	5.309	1.00	42.63	AI
ATOM	213	CA	LEU	32	36.226	65.019	4.167	1.00	32.94	AI	ATOM	264	II	CYS	37	29.250	62.904	5.020	1.00	0.00	AI
ATOM	214	CG	LEU	32	35.658	66.472	4.091	1.00	32.54	AI	ATOM	265	CA	CYS	37	27.216	62.469	5.084	1.00	43.53	AI
ATOM	215	CD1	LEU	32	35.516	67.082	5.499	1.00	32.87	AI	ATOM	266	C	CYS	37	26.638	62.026	6.362	1.00	44.65	AI
ATOM	216	CD2	LEU	32	36.535	67.267	3.181	1.00	30.97	AI	ATOM	267	O	CYS	37	25.426	61.997	6.459	1.00	46.40	AI
ATOM	217	C	LEU	32	34.133	63.597	4.318	1.00	27.87	AI	ATOM	268	CB	CYS	37	27.474	61.240	4.313	1.00	44.00	AI
ATOM	218	O	LEU	32	33.169	63.889	5.250	1.00	25.93	AI	ATOM	269	SG	CYS	37	26.133	60.038	4.530	1.00	43.86	AI
ATOM	219	N	GLN	33	33.977	63.028	3.315	1.00	27.51	AI	ATOM	270	N	ALA	38	27.465	61.734	7.342	1.00	45.96	AI
ATOM	220	H	GLN	33	34.787	62.826	2.802	1.00	0.00	AI	ATOM	271	II	ALA	38	28.433	61.707	7.202	1.00	0.00	AI
ATOM	221	CB	GLN	33	32.737	61.721	1.614	1.00	29.47	AI	ATOM	272	CA	ALA	38	26.932	61.261	8.592	1.00	48.03	AI
ATOM	222	CB	GLN	33	32.737	61.721	1.614	1.00	29.47	AI	ATOM	273	CB	ALA	38	27.869	60.140	9.108	1.00	48.64	AI
ATOM	223	CG	GLN	33	32.888	62.584	0.436	1.00	29.26	AI	ATOM	274	C	ALA	38	26.748	62.358	9.624	1.00	48.89	AI
ATOM	224	CD	GLN	33	33.015	61.869	0.887	1.00	30.21	AI	ATOM	275	O	ALA	38	26.103	62.085	10.621	1.00	50.72	AI
ATOM	225	O	GLN	33	34.064	61.495	-1.452	1.00	29.61	AI	ATOM	276	N	THR	39	27.256	63.590	9.512	1.00	50.66	AI
ATOM	226	NE2	GLN	33	31.823	61.759	-1.426	1.00	33.19	AI	ATOM	277	II	THR	39	27.858	63.780	8.770	1.00	0.00	AI
ATOM	227	HE21	GLN	34	31.781	61.328	-2.302	1.00	0.00	AI	ATOM	278	CA	THR	39	26.976	64.638	10.503	1.00	51.54	AI
ATOM	228	HE22	GLN	34	31.042	62.060	-0.914	1.00	0.00	AI	ATOM	279	CB	THR	39	28.179	65.593	10.690	1.00	51.76	AI
ATOM	229	C	GLN	33	31.839	61.963	3.788	1.00	35.60	AI	ATOM	280	CG1	THR	39	29.794	64.826	11.126	1.00	52.45	AI
ATOM	230	O	GLN	33	30.715	62.416	4.073	1.00	36.49	AI	ATOM	281	HG1	THR	39	29.749	64.481	10.355	1.00	0.00	AI
ATOM	231	N	GLU	34	32.386	60.925	4.438	1.00	39.81	AI	ATOM	282	CG2	THR	39	27.900	66.655	11.729	1.00	51.62	AI
ATOM	232	H	GLU	34	33.340	60.707	4.328	1.00	0.00	AI	ATOM	283	C	THR	39	25.775	65.466	10.037	1.00	52.17	AI
ATOM	233	CA	GLU	34	31.541	60.131	5.304	1.00	43.24	AI	ATOM	284	O	THR	39	24.886	65.882	10.781	1.00	52.15	AI
ATOM	234	CB	GLU	34	32.228	58.792	5.571	1.00	46.46	AI	ATOM	285	N	TYR	40	25.751	65.720	8.238	1.00	0.00	AI
ATOM	235	CG	GLU	34	33.274	58.721	6.624	1.00	55.01	AI	ATOM	286	H	TYR	40	26.420	65.331	8.139	1.00	0.00	AI
ATOM	236	CD	GLU	34	32.777	58.092	7.930	1.00	60.29	AI	ATOM	287	CA	TYR	40	24.779	66.561	8.165	1.00	52.53	AI
ATOM	237	O	GLU	34	33.483	57.186	8.412	1.00	63.26	AI	ATOM	288	CB	TYR	40	25.314	67.872	7.696	1.00	52.15	AI
ATOM	238	O	GLU	34	31.724	58.504	8.459	1.00	60.44	AI	ATOM	289	CG	TYR	40	26.399	68.458	8.552	1.00	54.11	AI
ATOM	239	C	GLU	34	31.218	60.877	6.564	1.00	43.59	AI	ATOM	290	CD1	TYR	40	27.678	68.341	8.062	1.00	56.50	AI
ATOM	240	O	GLU	34	30.175	60.631	7.161	1.00	44.87	AI	ATOM	291	CE1	TYR	40	28.719	68.934	8.724	1.00	58.28	AI
ATOM	241	N	LYS	35	32.045	61.811	6.998	1.00	44.80	AI	ATOM	292	CD2	TYR	40	26.122	69.144	9.714	1.00	54.86	AI
ATOM	242	H	LYS	35	32.923	61.931	6.369	1.00	0.00	AI	ATOM	293	CE2	TYR	40	27.170	69.746	10.378	1.00	56.20	AI
ATOM	243	CA	LYS	35	31.674	62.634	8.134	1.00	45.43	AI	ATOM	294	CZ	TYR	40	28.453	69.642	9.872	1.00	58.26	AI
ATOM	244	CB	LYS	35	32.881	63.364	8.686	1.00	47.67	AI	ATOM	295	CH	TYR	40	29.513	70.310	10.463	1.00	61.00	AI
ATOM	245	CG	LYS	35	33.701	62.414	9.510	1.00	52.75	AI	ATOM	296	HH	TYR	40	30.179	70.443	9.782	1.00	0.00	AI
ATOM	246	CD	LYS	35	35.084	63.021	9.548	1.00	57.55	AI	ATOM	297	C	TYR	40	24.035	65.911	6.981	1.00	51.75	AI
ATOM	247	CE	LYS	35	36.067	62.099	10.238	1.00	60.35	AI	ATOM	298	O	TYR	40	23.662	66.578	6.024	1.00	52.52	AI
ATOM	248	NZ	LYS	35	35.810	62.064	11.669	1.00	61.91	AI	ATOM	299	N	LYS	41	23.941	64.600	6.965	1.00	50.54	AI
ATOM	249	HZ1	LYS	35	34.838	61.733	11.840	1.00	0.00	AI	ATOM	300	H	LYS	41	24.474	64.064	7.583	1.00	0.00	AI
ATOM	250	HZ2	LYS	35	35.930	63.011	12.078	1.00	0.00	AI	ATOM	301	CA	LYS	41	23.112	63.885	6.029	1.00	50.48	AI
ATOM	251	HZ3	LYS	35	36.477	61.405	12.119	1.00	0.00	AI	ATOM	302	CB	LYS	41	21.641	63.989	6.540	1.00	50.62	AI
ATOM	252	C	LYS	35	30.630	63.660	7.697	1.00	44.45	AI	ATOM	303	CG	LYS	41	21.387	63.326	7.911	1.00	52.11	AI
ATOM	253	O	LYS	35	29.730	63.999	8.478	1.00	44.61	AI	ATOM	304	CD	LYS	41	20.112	63.878	8.574	1.00	55.54	AI

FIGURE 5

ATOM	305	CE IYS	41	19.578	63.087	9.820	1.00	58.79	A1	ATOM	356	C GLU	46	23.181	65.584	-6.937	1.00	42.96	A1
ATOM	306	NZ IYS	41	18.374	63.648	10.457	1.00	58.31	A1	ATOM	357	O GLU	46	22.932	66.223	-7.748	1.00	41.71	A1
ATOM	307	II21 IYS	41	17.605	63.688	9.757	1.00	0.00	A1	ATOM	358	N GLU	47	22.919	65.263	-5.564	1.00	41.96	A1
ATOM	308	II22 IYS	41	18.578	64.607	10.803	1.00	0.00	A1	ATOM	359	H GLU	47	23.507	65.098	-5.028	1.00	0.00	A1
ATOM	309	II23 IYS	41	18.084	63.043	11.252	1.00	0.00	A1	ATOM	360	CA GLU	47	21.818	66.301	-5.144	1.00	-3.71	A1
ATOM	310	C IYS	41	23.251	64.318	4.588	1.00	49.92	A1	ATOM	361	CB GLU	47	21.794	65.487	-3.963	1.00	41.74	A1
ATOM	311	O IYS	41	22.312	64.124	3.793	1.00	51.49	A1	ATOM	362	CG GLU	47	20.812	64.907	-1.547	1.00	40.86	A1
ATOM	312	N LEU	42	24.532	64.893	4.246	1.00	48.28	A1	ATOM	363	CD GLU	47	19.847	64.225	-1.910	1.00	50.99	A1
ATOM	313	H LEU	42	25.103	65.050	4.937	1.00	0.00	A1	ATOM	364	OEI GLU	47	21.313	64.780	-4.809	1.00	49.47	A1
ATOM	314	CA LEU	42	24.742	65.286	2.859	1.00	46.61	A1	ATOM	365	OEZ GLU	47	22.295	67.718	-4.809	1.00	49.47	A1
ATOM	315	CB LEU	42	25.565	66.574	2.757	1.00	44.69	A1	ATOM	366	C GLU	47	21.532	68.547	-4.292	1.00	44.60	A1
ATOM	316	CG LEU	42	24.807	67.802	3.218	1.00	42.63	A1	ATOM	367	O GLU	47	23.567	68.015	-5.121	1.00	43.05	A1
ATOM	317	CD1 LEU	42	25.178	68.580	4.097	1.00	43.29	A1	ATOM	368	H LEU	48	24.140	67.310	-5.465	1.00	0.00	A1
ATOM	318	CD2 LEU	42	24.283	68.590	2.045	1.00	41.26	A1	ATOM	369	N LEU	48	24.166	69.318	-4.904	1.00	42.42	A1
ATOM	319	C LEU	42	25.380	64.124	2.397	1.00	45.46	A1	ATOM	370	CA LEU	48	25.223	69.201	-3.858	1.00	40.55	A1
ATOM	320	O LEU	42	26.766	64.017	2.711	1.00	46.32	A1	ATOM	371	CB LEU	48	24.920	68.695	-2.489	1.00	41.87	A1
ATOM	321	N CYS	43	24.882	63.193	1.754	1.00	44.09	A1	ATOM	372	CG LEU	48	26.277	68.424	-1.892	1.00	41.71	A1
ATOM	322	H CYS	43	23.935	63.353	1.619	1.00	0.00	A1	ATOM	373	CD1 LEU	48	24.096	69.670	-1.633	1.00	41.13	A1
ATOM	323	CA CYS	43	25.480	61.951	1.358	1.00	42.87	A1	ATOM	374	CD2 LEU	48	24.792	69.937	-6.166	1.00	42.37	A1
ATOM	324	C CYS	43	25.448	61.846	-0.123	1.00	41.62	A1	ATOM	375	C LEU	48	24.792	69.937	-6.166	1.00	42.37	A1
ATOM	325	O CYS	43	25.762	60.803	-0.666	1.00	41.77	A1	ATOM	376	O LEU	48	25.439	70.994	-6.098	1.00	42.37	A1
ATOM	326	CB CYS	43	24.716	60.796	2.026	1.00	41.99	A1	ATOM	377	N VAL	49	24.566	69.366	-7.347	1.00	41.52	A1
ATOM	327	CG CYS	43	24.523	61.011	3.835	1.00	45.91	A1	ATOM	378	H VAL	49	23.951	68.602	-7.362	1.00	0.00	A1
ATOM	328	N IIS	44	25.057	62.846	-0.882	1.00	42.90	A1	ATOM	379	CA VAL	49	25.191	69.822	-8.578	1.00	43.44	A1
ATOM	329	H IIS	44	24.841	63.721	-0.491	1.00	0.00	A1	ATOM	380	CB VAL	49	24.890	68.761	-9.636	1.00	44.79	A1
ATOM	330	CA IIS	44	25.069	62.660	-2.320	1.00	44.60	A1	ATOM	381	CG VAL	49	23.381	68.709	-9.830	1.00	47.50	A1
ATOM	331	CG IIS	44	23.653	62.264	-2.825	1.00	48.40	A1	ATOM	382	CD2 VAL	49	25.540	69.086	-10.975	1.00	45.25	A1
ATOM	332	CG IIS	44	23.085	60.935	-2.310	1.00	50.37	A1	ATOM	383	C VAL	49	24.740	71.214	-9.028	1.00	44.98	A1
ATOM	333	CD1 IIS	44	22.178	60.844	-1.272	1.00	50.52	A1	ATOM	384	O VAL	49	25.401	71.901	-9.814	1.00	46.03	A1
ATOM	334	NDI IIS	44	23.558	59.689	-2.713	1.00	52.28	A1	ATOM	385	N LEU	50	23.565	71.602	-8.530	1.00	46.10	A1
ATOM	335	NDI IIS	44	24.130	59.394	-3.251	1.00	0.00	A1	ATOM	386	N LEU	50	23.081	70.933	-8.006	1.00	0.00	A1
ATOM	336	CEI IIS	44	22.632	58.873	-1.955	1.00	51.92	A1	ATOM	387	CA LEU	50	22.908	72.095	-8.729	1.00	46.03	A1
ATOM	337	NEI IIS	44	21.947	59.585	-1.091	1.00	50.53	A1	ATOM	388	CB LEU	50	21.469	72.769	-8.264	1.00	46.43	A1
ATOM	338	HEI IIS	44	21.920	59.189	-0.466	1.00	0.00	A1	ATOM	389	CG LEU	50	20.443	73.718	-8.760	1.00	44.16	A1
ATOM	339	C IIS	44	25.522	63.941	-3.047	1.00	43.69	A1	ATOM	390	CD1 LEU	50	20.259	73.558	-10.243	1.00	44.79	A1
ATOM	339	O IIS	44	24.765	64.906	-3.168	1.00	43.07	A1	ATOM	391	CD2 LEU	50	19.159	73.400	-8.079	1.00	44.66	A1
ATOM	341	N PRO	45	26.710	63.978	-3.667	1.00	43.07	A1	ATOM	392	C LEU	50	23.632	73.964	-7.917	1.00	45.85	A1
ATOM	342	CD PRO	45	27.785	62.995	-3.501	1.00	42.17	A1	ATOM	393	O LEU	50	23.996	74.989	-8.484	1.00	44.52	A1
ATOM	343	CA PRO	45	27.133	63.024	-4.570	1.00	42.50	A1	ATOM	394	N LEU	51	23.853	73.764	-6.606	1.00	45.44	A1
ATOM	344	CB PRO	45	28.380	64.466	-5.217	1.00	39.76	A1	ATOM	395	H LEU	51	23.853	72.958	-6.189	1.00	0.00	A1
ATOM	345	CG PRO	45	28.995	63.680	-4.123	1.00	39.09	A1	ATOM	396	CA LEU	51	24.676	74.656	-5.805	1.00	46.04	A1
ATOM	346	C PRO	45	26.071	65.423	-5.585	1.00	44.49	A1	ATOM	397	CB LEU	51	24.860	74.084	-4.435	1.00	45.53	A1
ATOM	347	O PRO	45	25.876	66.612	-5.801	1.00	45.36	A1	ATOM	398	CG LEU	51	25.741	74.931	-3.535	1.00	47.78	A1
ATOM	348	N GLU	46	25.334	64.501	-6.275	1.00	45.36	A1	ATOM	399	CD1 LEU	51	25.148	76.370	-3.322	1.00	47.13	A1
ATOM	349	H GLU	46	25.464	63.561	-5.996	1.00	0.00	A1	ATOM	400	CD2 LEU	51	25.902	74.702	-2.219	1.00	48.33	A1
ATOM	350	CA GLU	46	24.406	64.806	-7.319	1.00	45.46	A1	ATOM	401	C LEU	51	26.064	74.845	-6.436	1.00	46.27	A1
ATOM	351	CB GLU	46	23.932	63.515	-7.997	1.00	50.54	A1	ATOM	402	O LEU	51	26.551	75.966	-6.612	1.00	47.62	A1
ATOM	352	CG GLU	46	24.462	63.460	-9.445	1.00	58.48	A1	ATOM	403	N GLY	52	26.702	73.736	-6.809	1.00	44.84	A1
ATOM	353	CD GLU	46	23.637	64.215	-10.516	1.00	64.93	A1	ATOM	404	II GLY	52	26.306	72.869	-6.578	1.00	0.00	A1
ATOM	354	OEI GLU	46	23.642	65.455	-10.516	1.00	68.55	A1	ATOM	405	CA GLY	52	27.989	73.758	-7.453	1.00	47.91	A1
ATOM	355	OEZ GLU	46	22.995	63.554	-11.332	1.00	68.31	A1	ATOM	406	C GLY	52	27.984	74.533	-8.750	1.00	47.47	A1

FIGURE 5

ATOM	407	O	GLY	52	28.853	75.364	-8.983	1.00	42.06	AI	458	G	PRO	58	37.187	73.599	-9.691	1.00	-49.75	AI
ATOM	408	N	HIS	53	27.047	74.307	-9.653	1.00	42.02	AI	459	N	TRP	59	37.030	72.927	-11.816	1.00	50.37	AI
ATOM	409	H	HIS	53	26.366	73.624	-9.471	1.00	0.00	AI	460	H	TRP	59	36.888	73.141	-12.760	1.00	0.00	AI
ATOM	410	CA	HIS	53	27.009	75.104	-10.861	1.00	42.23	AI	461	CA	TRP	59	37.524	71.595	-11.482	1.00	51.78	AI
ATOM	411	CB	HIS	53	25.842	74.689	-11.706	1.00	42.21	AI	462	CB	TRP	59	36.435	70.562	-11.857	1.00	-49.06	AI
ATOM	412	CG	HIS	53	26.076	73.399	-12.460	1.00	44.60	AI	463	CG	TRP	59	35.254	70.712	-10.889	1.00	-46.37	AI
ATOM	413	CD2	HIS	53	25.112	72.774	-13.200	1.00	47.49	AI	464	CD2	TRP	59	35.370	70.845	-9.521	1.00	-44.06	AI
ATOM	414	ND1	HIS	53	27.180	72.669	-12.578	1.00	46.76	AI	465	CD2	TRP	59	33.998	71.027	-9.205	1.00	-44.18	AI
ATOM	415	CE1	HIS	53	26.954	71.641	-13.346	1.00	46.90	AI	466	CE2	TRP	59	36.274	70.842	-8.538	1.00	-44.03	AI
ATOM	416	CE1	HIS	53	28.039	72.853	-12.139	1.00	0.00	AI	467	CD1	TRP	59	33.972	70.794	-11.354	1.00	-45.17	AI
ATOM	417	NE2	HIS	53	25.704	71.725	-13.707	1.00	50.22	AI	468	NE1	TRP	59	33.229	70.994	-10.297	1.00	-43.17	AI
ATOM	418	NE2	HIS	53	25.237	71.033	-14.239	1.00	0.00	AI	469	NE1	TRP	59	32.301	71.312	-10.332	1.00	0.00	AI
ATOM	419	C	HIS	53	26.893	76.585	-10.536	1.00	42.72	AI	470	CD2	TRP	59	33.598	71.215	-7.916	1.00	-45.40	AI
ATOM	420	O	HIS	53	27.622	77.399	-11.068	1.00	42.03	AI	471	CZ2	TRP	59	35.893	71.028	-7.243	1.00	-45.25	AI
ATOM	421	N	SER	54	26.099	76.920	-9.535	1.00	45.08	AI	472	C12	TRP	59	34.565	71.214	-6.938	1.00	-46.43	AI
ATOM	422	H	SER	54	25.673	76.218	-9.001	1.00	0.00	AI	473	C	TRP	59	38.815	71.435	-12.256	1.00	52.84	AI
ATOM	423	CA	SER	54	24.576	78.181	-8.289	1.00	48.86	AI	474	O	TRP	59	38.842	71.972	-13.372	1.00	54.96	AI
ATOM	424	CB	SER	54	23.521	77.616	-9.112	1.00	53.06	AI	475	N	ALA	60	39.912	70.834	-11.777	1.00	51.97	AI
ATOM	425	OG	SER	54	23.465	76.677	-8.918	1.00	0.00	AI	476	H	ALA	60	39.857	70.269	-10.977	1.00	0.00	AI
ATOM	426	HC	SER	54	26.939	79.033	-8.549	1.00	47.92	AI	477	CA	ALA	60	41.108	70.870	-12.609	1.00	52.18	AI
ATOM	427	C	SER	54	27.038	80.264	-8.655	1.00	49.60	AI	478	CB	ALA	60	42.303	70.610	-11.748	1.00	51.75	AI
ATOM	428	O	SER	54	27.837	78.273	-7.933	1.00	47.59	AI	479	C	ALA	60	41.055	69.857	-13.746	1.00	52.16	AI
ATOM	429	N	LEU	55	27.638	77.322	-7.791	1.00	0.00	AI	480	O	ALA	60	40.545	68.760	-13.530	1.00	52.17	AI
ATOM	430	H	LEU	55	29.075	78.810	-7.401	1.00	45.27	AI	481	N	PRO	61	41.435	70.145	-14.986	1.00	51.14	AI
ATOM	431	CA	LEU	55	29.552	77.913	-6.243	1.00	45.49	AI	482	CD	PRO	61	41.370	71.458	-15.622	1.00	54.76	AI
ATOM	432	CB	LEU	55	28.840	77.992	-6.874	1.00	47.30	AI	483	CA	PRO	61	41.691	69.145	-15.993	1.00	55.57	AI
ATOM	433	CG	LEU	55	28.876	76.596	-4.799	1.00	45.52	AI	484	CB	PRO	61	41.792	69.918	-17.310	1.00	54.95	AI
ATOM	434	CD1	LEU	55	30.133	78.889	-8.492	1.00	43.63	AI	485	CG	PRO	61	42.211	71.297	-16.901	1.00	54.05	AI
ATOM	435	CD2	LEU	55	29.530	78.921	-3.862	1.00	45.69	AI	486	C	PRO	61	42.934	68.333	-15.690	1.00	57.54	AI
ATOM	436	C	LEU	55	31.247	79.350	-8.272	1.00	43.24	AI	487	O	PRO	61	43.757	68.661	-14.834	1.00	57.20	AI
ATOM	437	O	LEU	55	29.855	78.383	-9.675	1.00	43.55	AI	488	N	LEU	62	43.040	67.271	-16.486	1.00	59.98	AI
ATOM	438	N	GLY	56	28.984	77.975	-9.828	1.00	0.00	AI	489	H	LEU	62	42.285	67.067	-17.077	1.00	0.00	AI
ATOM	439	H	GLY	56	30.814	78.390	-10.753	1.00	45.59	AI	490	CA	LEU	62	44.184	66.370	-16.471	1.00	63.64	AI
ATOM	440	C	GLY	56	32.182	77.811	-10.392	1.00	46.76	AI	491	CB	LEU	62	44.062	65.417	-15.260	1.00	63.72	AI
ATOM	441	O	GLY	56	33.171	78.213	-11.015	1.00	47.31	AI	492	CG	LEU	62	46.394	65.704	-14.488	1.00	64.43	AI
ATOM	442	N	ILE	57	32.247	76.885	-9.412	1.00	47.49	AI	493	CD1	LEU	62	45.323	64.591	-14.865	1.00	64.43	AI
ATOM	443	H	ILE	57	31.392	76.594	-9.042	1.00	0.00	AI	494	CD2	LEU	62	45.016	63.764	-13.717	1.00	64.98	AI
ATOM	444	H	ILE	57	33.486	76.249	-8.950	1.00	48.28	AI	495	C	LEU	62	44.214	65.611	-17.812	1.00	65.69	AI
ATOM	445	CA	ILE	57	33.144	75.172	-7.863	1.00	47.79	AI	496	OT1	LEU	62	44.256	66.302	-18.844	1.00	66.57	AI
ATOM	446	CB	ILE	57	34.457	74.591	-7.348	1.00	46.85	AI	497	OT2	LEU	62	44.194	64.371	-17.845	1.00	66.57	AI
ATOM	447	CG2	ILE	57	32.338	75.764	-6.701	1.00	45.09	AI	498	CB	LEU	72	57.448	63.159	-19.422	1.00	63.40	AI
ATOM	448	CG1	ILE	57	31.859	74.739	-5.659	1.00	41.23	AI	499	CG	LEU	72	57.716	62.495	-18.117	1.00	63.40	AI
ATOM	449	CD	ILE	57	34.276	75.602	-10.115	1.00	49.15	AI	500	CD1	LEU	72	56.719	61.400	-17.913	1.00	61.50	AI
ATOM	450	C	ILE	57	33.678	74.935	-10.968	1.00	49.04	AI	501	CD2	LEU	72	59.107	61.901	-18.121	1.00	63.22	AI
ATOM	451	O	ILE	57	35.596	75.817	-10.248	1.00	49.75	AI	502	C	LEU	72	55.897	65.084	-18.076	1.00	65.40	AI
ATOM	452	N	PRO	58	36.402	76.743	-9.433	1.00	50.94	AI	503	O	LEU	72	54.827	65.301	-18.316	1.00	67.40	AI
ATOM	453	CD	PRO	58	36.421	75.228	-11.302	1.00	50.72	AI	504	IIT1	LEU	72	56.469	64.683	-21.261	1.00	0.00	AI
ATOM	454	CA	PRO	58	37.525	76.241	-11.488	1.00	50.92	AI	505	IIT2	LEU	72	54.827	64.355	-20.951	1.00	0.00	AI
ATOM	455	CB	PRO	58	37.814	76.663	-10.041	1.00	50.82	AI	506	N	LEU	72	55.795	63.983	-20.899	1.00	66.29	AI
ATOM	456	CG	PRO	58	36.916	73.845	-10.875	1.00	50.36	AI	507	IIT3	LEU	72	55.866	63.098	-21.439	1.00	0.00	AI
ATOM	457	C	PRO	58						AI	508	CA	LEU	72	56.064	63.714	-19.512	1.00	64.91	AI

FIGURE 5

ATOM	509	N	ALA	73	56.807	66.046	-19.086	1.00	64.54	A2	560	CG	LEU	79	49.154	64.895	-11.351	1.00	45.18	A2
ATOM	510	II	ALA	73	57.690	65.804	-19.432	1.00	0.00	A2	561	CD1	LEU	79	49.634	63.594	-11.957	1.00	45.18	A2
ATOM	511	CA	ALA	73	56.707	67.433	-18.615	1.00	62.55	A2	562	CD2	LEU	79	49.766	64.986	-9.969	1.00	46.03	A2
ATOM	512	CB	ALA	73	57.553	68.314	-19.529	1.00	60.84	A2	563	C	LEU	79	49.366	68.265	-11.170	1.00	43.49	A2
ATOM	513	C	ALA	73	55.319	68.024	-18.539	1.00	64.37	A2	564	O	LEU	79	48.645	68.509	-10.199	1.00	43.20	A2
ATOM	514	O	ALA	73	54.801	68.180	-17.456	1.00	59.42	A2	565	II	HIS	80	50.536	68.834	-11.329	1.00	43.83	A2
ATOM	515	N	GLY	74	54.693	68.226	-19.691	1.00	59.72	A2	566	II	HIS	80	51.115	68.548	-12.085	1.00	0.00	A2
ATOM	516	H	GLY	74	55.212	68.174	-20.514	1.00	0.00	A2	567	CA	HIS	80	51.060	69.788	-10.360	1.00	43.79	A2
ATOM	517	CA	GLY	74	53.336	68.728	-19.816	1.00	59.99	A2	568	CB	HIS	80	52.456	70.221	-10.810	1.00	43.58	A2
ATOM	518	C	GLY	74	52.327	68.114	-18.865	1.00	60.27	A2	569	CG	HIS	80	53.030	71.031	-9.690	1.00	44.75	A2
ATOM	519	O	GLY	74	51.880	68.796	-17.935	1.00	60.80	A2	570	CD2	HIS	80	53.484	70.497	-8.517	1.00	47.48	A2
ATOM	520	N	CYS	75	51.945	66.850	-19.030	1.00	59.60	A2	571	ND1	HIS	80	53.083	72.343	-9.567	1.00	44.24	A2
ATOM	521	H	CYS	75	52.160	66.358	-19.839	1.00	0.00	A2	572	HD1	HIS	80	52.842	73.004	-10.255	1.00	0.00	A2
ATOM	522	CA	CYS	75	51.002	66.276	-18.078	1.00	60.17	A2	573	CE1	HIS	80	53.330	72.641	-8.376	1.00	44.47	A2
ATOM	523	CB	CYS	75	50.670	64.801	-18.464	1.00	64.08	A2	574	NE2	HIS	80	53.772	71.520	-7.748	1.00	48.16	A2
ATOM	524	SG	CYS	75	49.832	64.732	-20.096	1.00	73.47	A2	575	HE2	HIS	80	54.103	71.444	-6.824	1.00	0.00	A2
ATOM	525	C	CYS	75	51.502	66.346	-16.642	1.00	56.73	A2	576	C	HIS	80	50.094	70.978	-10.229	1.00	44.40	A2
ATOM	526	O	CYS	75	50.734	66.748	-15.765	1.00	55.82	A2	577	O	HIS	80	49.643	71.294	-9.131	1.00	44.28	A2
ATOM	527	N	LEU	76	52.795	66.142	-16.396	1.00	53.93	A2	578	N	SER	81	49.733	71.670	-11.309	1.00	45.13	A2
ATOM	528	H	LEU	76	53.423	66.043	-17.137	1.00	0.00	A2	579	H	SER	81	50.136	71.459	-12.176	1.00	0.00	A2
ATOM	529	CA	LEU	76	53.325	66.156	-15.044	1.00	52.94	A2	580	CA	SER	81	48.738	72.742	-11.296	1.00	45.41	A2
ATOM	530	CB	LEU	76	54.798	65.754	-15.181	1.00	50.81	A2	581	CB	SER	81	48.612	73.347	-12.682	1.00	45.59	A2
ATOM	531	CG	LEU	76	55.575	65.011	-14.090	1.00	49.02	A2	582	OG	SER	81	50.058	72.670	-13.843	1.00	0.00	A2
ATOM	532	CD1	LEU	76	54.852	63.740	-13.698	1.00	46.76	A2	583	IG	SER	81	47.344	72.766	-10.856	1.00	44.85	A2
ATOM	533	CD2	LEU	76	56.951	64.633	-14.623	1.00	47.67	A2	584	O	SER	81	46.604	73.064	-10.256	1.00	46.53	A2
ATOM	534	C	LEU	76	53.093	67.345	-14.425	1.00	53.65	A2	585	O	SER	81	46.946	71.010	-11.092	1.00	42.16	A2
ATOM	535	O	LEU	76	52.731	67.716	-13.244	1.00	53.50	A2	586	N	GLY	82	46.946	71.010	-11.092	1.00	42.16	A2
ATOM	536	N	SER	77	53.137	68.553	-15.301	1.00	53.91	A2	587	H	GLY	82	47.513	70.411	-11.614	1.00	0.00	A2
ATOM	537	H	SER	77	53.322	68.361	-16.242	1.00	0.00	A2	588	CA	GLY	82	45.663	70.500	-10.650	1.00	39.49	A2
ATOM	538	CA	SER	77	52.882	69.932	-14.942	1.00	54.93	A2	589	O	GLY	82	45.569	70.461	-9.139	1.00	59.40	A2
ATOM	539	CB	SER	77	53.425	70.835	-16.040	1.00	58.32	A2	590	O	GLY	82	44.542	70.843	-8.544	1.00	59.64	A2
ATOM	540	OG	SER	77	54.806	70.587	-16.310	1.00	63.35	A2	591	N	LEU	83	46.676	70.032	-8.521	1.00	37.57	A2
ATOM	541	HG	SER	77	54.949	69.637	-16.315	1.00	0.00	A2	592	H	LEU	83	47.413	69.695	-9.075	1.00	0.00	A2
ATOM	542	C	SER	77	51.382	70.172	-14.759	1.00	53.47	A2	593	CA	LEU	83	46.826	70.007	-7.051	1.00	38.07	A2
ATOM	543	O	SER	77	50.982	70.965	-13.899	1.00	53.54	A2	594	CB	LEU	83	48.133	69.202	-6.748	1.00	35.67	A2
ATOM	544	N	GLN	78	50.509	69.501	-15.512	1.00	51.82	A2	595	CG	LEU	83	48.071	67.736	-7.275	1.00	32.51	A2
ATOM	545	H	GLN	78	50.857	68.901	-16.207	1.00	0.00	A2	596	CD1	LEU	83	49.442	67.145	-7.319	1.00	29.77	A2
ATOM	546	CA	GLN	78	49.074	69.619	-15.349	1.00	50.74	A2	597	CD2	LEU	83	47.180	66.973	-6.288	1.00	28.71	A2
ATOM	547	CB	GLN	78	48.402	68.877	-16.451	1.00	54.31	A2	598	C	LEU	83	46.836	71.386	-6.354	1.00	38.49	A2
ATOM	548	CG	GLN	78	47.420	69.784	-17.160	1.00	58.59	A2	599	O	LEU	83	46.392	71.627	-5.219	1.00	38.05	A2
ATOM	549	CD	GLN	78	46.557	68.940	-18.071	1.00	62.32	A2	600	H	PIE	84	47.366	72.338	-7.108	1.00	40.34	A2
ATOM	550	OE1	GLN	78	47.005	68.260	-18.998	1.00	63.94	A2	601	H	PIE	84	47.804	72.078	-7.944	1.00	0.00	A2
ATOM	551	NE2	GLN	78	45.769	68.889	-17.800	1.00	63.17	A2	602	CA	PIE	84	47.414	73.703	-6.688	1.00	41.54	A2
ATOM	552	HE1	GLN	78	44.973	69.327	-16.972	1.00	0.00	A2	603	CB	PIE	84	48.163	74.531	-7.693	1.00	43.88	A2
ATOM	553	HE2	GLN	78	44.704	68.444	-18.456	1.00	0.00	A2	604	CG	PIE	84	48.715	75.777	-6.988	1.00	55.03	A2
ATOM	554	C	GLN	78	48.591	69.065	-14.011	1.00	48.17	A2	605	CD1	PIE	84	49.521	75.622	-5.849	1.00	55.41	A2
ATOM	555	O	GLN	78	47.691	69.618	-13.368	1.00	46.31	A2	606	CD2	PIE	84	48.396	77.053	-7.469	1.00	55.79	A2
ATOM	556	N	LEU	79	49.236	67.988	-13.564	1.00	45.89	A2	607	CE1	PIE	84	50.004	76.737	-5.195	1.00	57.60	A2
ATOM	557	H	LEU	79	49.920	67.584	-14.140	1.00	0.00	A2	608	CE2	PIE	84	48.892	78.156	-6.796	1.00	57.25	A2
ATOM	558	CA	LEU	79	48.919	67.359	-12.294	1.00	44.54	A2	609	C2	PIE	84	49.688	78.002	-5.667	1.00	58.44	A2
ATOM	559	CB	LEU	79	49.617	66.015	-12.259	1.00	45.06	A2	610	C	PIE	84	45.994	74.191	-6.531	1.00	40.47	A2

FIGURE 5

ATOM	815	CB	GLN	108	45.138	71.363	3.630	1.00	30.15	A2	ATOM	866	II	PIIE	114	51.344	66.164	-1.361	1.00	0.00	A2
ATOM	816	CG	GLN	108	43.711	71.787	3.542	1.00	32.67	A2	ATOM	867	CA	PIIE	114	52.109	65.328	-3.103	1.00	27.84	A2
ATOM	817	CD	GLN	108	43.606	73.192	4.048	1.00	35.24	A2	ATOM	868	CB	PIIE	114	50.708	64.794	-3.226	1.00	23.18	A2
ATOM	818	CEI	GLN	108	43.085	73.484	5.125	1.00	36.07	A2	ATOM	869	CG	PIIE	114	50.565	63.928	-4.420	1.00	21.04	A2
ATOM	819	NEI	GLN	108	44.189	74.044	5.125	1.00	33.58	A2	ATOM	870	CDI	PIIE	114	51.623	63.225	-4.938	1.00	24.05	A2
ATOM	820	HEI2	GLN	108	44.582	73.701	2.386	1.00	0.00	A2	ATOM	871	CDI	PIIE	114	49.369	63.914	-5.046	1.00	22.37	A2
ATOM	821	HEI2	GLN	108	44.195	74.986	3.471	1.00	0.00	A2	ATOM	872	CEI	PIIE	114	51.476	62.514	-6.102	1.00	24.54	A2
ATOM	822	C	GLN	108	46.840	69.842	2.675	1.00	26.40	A2	ATOM	873	CEI	PIIE	114	49.211	63.207	-6.212	1.00	21.33	A2
ATOM	823	O	GLN	108	47.450	69.955	1.597	1.00	27.57	A2	ATOM	874	CZ	PIIE	114	50.263	62.509	-6.741	1.00	24.71	A2
ATOM	824	N	LEU	109	47.388	69.473	3.833	1.00	25.81	A2	ATOM	875	C	PIIE	114	52.453	66.291	-4.190	1.00	29.20	A2
ATOM	825	II	LEU	109	46.795	69.495	4.615	1.00	0.00	A2	ATOM	876	O	PIIE	114	53.072	65.883	-5.158	1.00	30.84	A2
ATOM	826	CA	LEU	109	48.764	69.003	4.043	1.00	27.96	A2	ATOM	877	N	ALA	115	52.057	67.554	-4.058	1.00	31.99	A2
ATOM	827	CB	LEU	109	48.951	68.637	5.513	1.00	29.41	A2	ATOM	878	II	ALA	115	51.446	67.768	-3.317	1.00	0.00	A2
ATOM	828	CG	LEU	109	48.712	69.771	6.520	1.00	31.78	A2	ATOM	879	CA	ALA	115	52.473	68.655	-4.952	1.00	31.29	A2
ATOM	829	CDI	LEU	109	48.750	69.188	7.933	1.00	29.16	A2	ATOM	880	CB	ALA	115	51.841	69.959	-4.420	1.00	30.65	A2
ATOM	830	CDI	LEU	109	49.724	70.189	6.285	1.00	32.19	A2	ATOM	881	C	ALA	115	53.936	68.787	-4.976	1.00	31.31	A2
ATOM	831	C	LEU	109	49.168	67.790	3.186	1.00	26.80	A2	ATOM	882	O	ALA	115	54.539	68.823	-6.044	1.00	30.36	A2
ATOM	832	O	LEU	109	50.214	67.721	2.544	1.00	26.81	A2	ATOM	883	N	THR	116	54.551	68.846	-3.813	1.00	32.20	A2
ATOM	833	N	ASP	110	48.305	66.807	3.090	1.00	25.98	A2	ATOM	884	II	THR	116	54.013	68.910	-2.992	1.00	0.00	A2
ATOM	834	H	ASP	110	47.471	66.835	3.600	1.00	0.00	A2	ATOM	885	CA	THR	116	55.998	68.897	-3.656	1.00	34.91	A2
ATOM	835	CA	ASP	110	48.590	65.684	2.250	1.00	23.32	A2	ATOM	886	CB	THR	116	56.323	68.953	-2.150	1.00	35.78	A2
ATOM	836	CB	ASP	110	47.577	64.570	2.553	1.00	26.34	A2	ATOM	887	CGI	THR	116	55.564	70.038	-1.576	1.00	35.58	A2
ATOM	837	CG	ASP	110	47.905	63.878	3.894	1.00	31.10	A2	ATOM	888	HGI	THR	116	54.942	69.644	-0.939	1.00	0.00	A2
ATOM	838	ONI	ASP	110	47.070	63.073	4.223	1.00	34.98	A2	ATOM	889	CGI	THR	116	57.816	69.050	-1.921	1.00	35.18	A2
ATOM	839	ONI	ASP	110	48.958	64.107	4.535	1.00	34.00	A2	ATOM	890	C	THR	116	56.714	67.726	-4.304	1.00	37.14	A2
ATOM	840	C	ASP	110	48.557	66.138	0.842	1.00	21.31	A2	ATOM	891	O	THR	116	57.641	67.937	-5.066	1.00	39.27	A2
ATOM	841	O	ASP	110	49.493	65.711	0.165	1.00	20.63	A2	ATOM	892	N	THR	117	56.318	66.485	-4.045	1.00	39.05	A2
ATOM	842	N	VAL	111	47.627	66.998	0.363	1.00	20.80	A2	ATOM	893	II	THR	117	55.615	66.383	-3.369	1.00	0.00	A2
ATOM	843	H	VAL	111	46.900	67.310	0.944	1.00	0.00	A2	ATOM	894	CA	THR	117	56.840	65.269	-4.630	1.00	40.23	A2
ATOM	844	CA	VAL	111	47.711	67.454	-1.019	1.00	20.44	A2	ATOM	895	CB	THR	117	55.909	64.090	-4.216	1.00	39.99	A2
ATOM	845	CB	VAL	111	46.531	68.364	-1.576	1.00	23.60	A2	ATOM	896	CGI	THR	117	56.149	63.920	-2.810	1.00	41.64	A2
ATOM	846	CGI	VAL	111	46.615	68.946	-2.808	1.00	23.04	A2	ATOM	897	HGI	THR	117	55.653	64.559	-2.286	1.00	0.00	A2
ATOM	847	CGI	VAL	111	45.289	67.497	-1.371	1.00	24.30	A2	ATOM	898	CGI	THR	117	56.110	62.781	-4.981	1.00	38.23	A2
ATOM	848	C	VAL	111	49.006	68.224	-1.245	1.00	20.82	A2	ATOM	899	C	THR	117	56.882	65.417	-6.134	1.00	43.42	A2
ATOM	849	O	VAL	111	49.617	68.006	-2.303	1.00	19.22	A2	ATOM	900	O	THR	117	57.934	65.253	-6.749	1.00	46.29	A2
ATOM	850	N	ALA	112	49.442	69.083	-0.267	1.00	21.84	A2	ATOM	901	N	ILE	118	55.763	65.777	-6.741	1.00	45.87	A2
ATOM	851	H	ALA	112	48.839	69.190	0.492	1.00	0.00	A2	ATOM	902	H	ILE	118	54.962	65.942	-6.200	1.00	0.00	A2
ATOM	852	CA	ALA	112	50.708	69.805	-0.295	1.00	24.16	A2	ATOM	903	CA	ILE	118	55.659	65.914	-8.182	1.00	47.97	A2
ATOM	853	CB	ALA	112	50.861	70.561	1.011	1.00	22.69	A2	ATOM	904	CB	ILE	118	54.170	66.271	-8.452	1.00	47.69	A2
ATOM	854	C	ALA	112	51.931	68.878	-0.486	1.00	28.58	A2	ATOM	905	CGI	ILE	118	54.041	66.930	-9.835	1.00	47.03	A2
ATOM	855	O	ALA	112	52.778	69.026	-1.390	1.00	32.53	A2	ATOM	906	CGI	ILE	118	53.302	65.011	-8.244	1.00	44.00	A2
ATOM	856	N	ASP	113	52.086	67.852	0.343	1.00	30.21	A2	ATOM	907	CD	ILE	118	53.651	63.883	-9.236	1.00	43.71	A2
ATOM	857	II	ASP	113	51.507	67.817	1.130	1.00	0.00	A2	ATOM	908	C	ILE	118	56.647	66.932	-8.724	1.00	50.69	A2
ATOM	858	CA	ASP	113	53.084	66.846	0.166	1.00	31.70	A2	ATOM	909	O	ILE	118	57.390	66.676	-9.681	1.00	49.98	A2
ATOM	859	CB	ASP	113	52.706	65.659	0.953	1.00	36.31	A2	ATOM	910	N	TRP	119	56.697	68.061	-8.015	1.00	54.66	A2
ATOM	860	CG	ASP	113	53.170	65.758	2.357	1.00	42.27	A2	ATOM	911	H	TRP	119	56.164	68.135	-7.197	1.00	0.00	A2
ATOM	861	ONI	ASP	113	52.559	65.109	3.203	1.00	46.37	A2	ATOM	912	CA	TRP	119	57.575	69.142	-8.399	1.00	58.98	A2
ATOM	862	ONI	ASP	113	54.160	66.461	2.589	1.00	48.93	A2	ATOM	913	CB	TRP	119	57.392	70.367	-7.477	1.00	59.84	A2
ATOM	863	C	ASP	113	53.315	66.361	-1.239	1.00	32.82	A2	ATOM	914	CG	TRP	119	58.051	71.529	-8.196	1.00	62.44	A2
ATOM	864	O	ASP	113	54.433	66.308	-1.754	1.00	36.25	A2	ATOM	915	CDI	TRP	119	57.596	72.211	-9.307	1.00	63.78	A2
ATOM	865	N	PIIE	114	52.187	65.978	-1.830	1.00	30.94	A2	ATOM	916	CEI	TRP	119	58.699	72.955	-9.643	1.00	62.55	A2

FIGURE 5

ATOM	917	CE3 TRP	119	56.465	72.314	-10.080	1.00	66.02	A2
ATOM	918	CD1 TRP	119	59.322	71.870	-7.863	1.00	64.12	A2
ATOM	919	NE1 TRP	119	59.680	72.727	-8.784	1.00	65.00	A2
ATOM	920	HE1 TRP	119	60.568	73.140	-8.828	1.00	0.00	A2
ATOM	921	C22 TRP	119	58.726	73.794	-10.714	1.00	62.90	A2
ATOM	922	C23 TRP	119	56.469	73.157	-11.170	1.00	65.18	A2
ATOM	923	CH2 TRP	119	57.591	73.887	-11.481	1.00	64.40	A2
ATOM	924	C TRP	119	59.021	68.664	-8.352	1.00	61.26	A2
ATOM	925	O TRP	119	59.748	68.786	-9.343	1.00	62.12	A2
ATOM	926	N GLN	120	59.447	68.065	-7.249	1.00	62.91	A2
ATOM	927	H GLN	120	58.811	67.961	-6.519	1.00	0.00	A2
ATOM	928	CA GLN	120	60.786	67.504	-7.113	1.00	65.16	A2
ATOM	929	CB GLN	120	60.900	66.800	-5.780	1.00	66.56	A2
ATOM	930	CG GLN	120	60.627	67.678	-4.582	1.00	67.18	A2
ATOM	931	CD GLN	120	60.725	66.907	-3.284	1.00	67.77	A2
ATOM	932	OE1 GLN	120	61.221	67.465	-2.319	1.00	69.31	A2
ATOM	933	NE2 GLN	120	60.305	65.654	-3.129	1.00	67.39	A2
ATOM	934	HE2 GLN	120	59.903	65.174	-3.877	1.00	0.00	A2
ATOM	935	HE2 GLN	120	60.441	65.282	-2.234	1.00	0.00	A2
ATOM	936	C GLN	120	61.169	66.509	-8.222	1.00	66.22	A2
ATOM	937	O GLN	120	62.326	66.421	-8.662	1.00	66.50	A2
ATOM	938	N GLN	121	60.202	65.745	-8.706	1.00	67.10	A2
ATOM	939	H GLN	121	59.307	65.754	-8.303	1.00	0.00	A2
ATOM	940	CA GLN	121	60.480	64.878	-9.812	1.00	68.66	A2
ATOM	941	CB GLN	121	59.292	63.971	-10.070	1.00	67.96	A2
ATOM	942	CG GLN	121	59.614	62.937	-11.128	1.00	68.89	A2
ATOM	943	CD GLN	121	60.940	62.236	-10.852	1.00	71.37	A2
ATOM	944	OE1 GLN	121	61.212	61.706	-9.777	1.00	71.70	A2
ATOM	945	NE2 GLN	121	61.879	62.262	-11.786	1.00	74.41	A2
ATOM	946	HE2 GLN	121	61.707	62.729	-12.627	1.00	0.00	A2
ATOM	947	HE2 GLN	121	62.736	61.859	-11.541	1.00	0.00	A2
ATOM	948	C GLN	121	60.760	65.743	-11.045	1.00	70.48	A2
ATOM	949	O GLN	121	61.671	65.436	-11.827	1.00	70.94	A2
ATOM	950	N MET	122	60.019	66.846	-11.236	1.00	71.67	A2
ATOM	951	H MET	122	59.351	67.087	-10.555	1.00	0.00	A2
ATOM	952	CA MET	122	60.190	67.688	-12.412	1.00	72.62	A2
ATOM	953	CB MET	122	59.173	68.819	-12.448	1.00	73.12	A2
ATOM	954	CG MET	122	57.880	68.343	-13.083	1.00	73.64	A2
ATOM	955	CD MET	122	56.669	69.642	-13.295	1.00	75.44	A2
ATOM	956	CE MET	122	55.695	69.349	-11.861	1.00	76.43	A2
ATOM	957	C MET	122	61.566	68.281	-12.411	1.00	73.22	A2
ATOM	958	O MET	122	62.240	68.287	-13.441	1.00	73.03	A2
ATOM	959	N GLU	123	61.991	68.697	-11.223	1.00	74.74	A2
ATOM	960	H GLU	123	61.372	68.617	-10.466	1.00	0.00	A2
ATOM	961	CA GLU	123	63.305	69.262	-11.018	1.00	75.95	A2
ATOM	962	CB GLU	123	63.484	69.665	-9.597	1.00	75.72	A2
ATOM	963	CG GLU	123	62.644	70.906	-9.500	1.00	79.11	A2
ATOM	964	CD GLU	123	62.651	71.579	-8.122	1.00	83.02	A2
ATOM	965	OE1 GLU	123	62.741	72.763	-8.057	1.00	84.15	A2
ATOM	966	OE2 GLU	123	62.543	70.789	-7.133	1.00	84.45	A2
ATOM	967	C GLU	123	64.381	68.280	-11.386	1.00	77.17	A2
ATOM	968	U GLU	123	65.092	68.558	-12.356	1.00	78.22	A2
ATOM	969	N GLU	124	64.504	67.110	-10.765	1.00	77.66	A2
ATOM	970	H GLU	124	63.867	66.852	-10.060	1.00	0.00	A2
ATOM	971	CA GLU	124	65.574	66.215	-11.167	1.00	78.47	A2
ATOM	972	CB GLU	124	65.600	65.051	-10.195	1.00	80.79	A2
ATOM	973	CG GLU	124	64.387	64.132	-10.150	1.00	83.29	A2
ATOM	974	CD GLU	124	64.375	63.248	-8.908	1.00	85.51	A2
ATOM	975	OE1 GLU	124	64.733	63.729	-7.824	1.00	86.84	A2
ATOM	976	OE2 GLU	124	64.006	62.075	-9.024	1.00	86.49	A2
ATOM	977	C GLU	124	65.534	65.705	-12.612	1.00	78.01	A2
ATOM	978	N LEU	125	64.460	65.057	-13.060	1.00	78.91	A2
ATOM	979	H LEU	125	64.460	65.943	-13.363	1.00	77.11	A2
ATOM	980	CA LEU	125	63.666	66.340	-12.945	1.00	0.00	A2
ATOM	981	CB LEU	125	64.387	65.583	-14.771	1.00	76.23	A2
ATOM	982	CG LEU	125	63.061	64.832	-14.952	1.00	76.88	A2
ATOM	983	CD LEU	125	62.392	64.382	-16.263	1.00	76.63	A2
ATOM	984	OE1 LEU	125	63.350	63.754	-17.276	1.00	76.67	A2
ATOM	985	OE2 LEU	125	61.309	63.402	-15.839	1.00	75.89	A2
ATOM	986	C LEU	125	64.506	66.827	-15.648	1.00	75.84	A2
ATOM	987	O LEU	125	64.360	66.788	-16.871	1.00	75.36	A2
ATOM	988	N GLY	126	64.759	67.968	-15.027	1.00	75.90	A2
ATOM	989	H GLY	126	64.741	67.976	-14.056	1.00	0.00	A2
ATOM	990	CA GLY	126	64.968	69.213	-15.736	1.00	77.58	A2
ATOM	991	CB GLY	126	63.677	69.814	-16.330	1.00	78.63	A2
ATOM	992	CG GLY	126	63.735	70.736	-17.146	1.00	78.55	A2
ATOM	993	O MET	127	62.524	69.343	-15.933	1.00	80.08	A2
ATOM	994	H MET	127	62.522	68.603	-15.293	1.00	0.00	A2
ATOM	995	CA MET	127	61.766	69.902	-16.415	1.00	81.46	A2
ATOM	996	CB MET	127	60.191	68.802	-16.361	1.00	81.86	A2
ATOM	997	CG MET	127	60.708	67.599	-17.147	1.00	82.66	A2
ATOM	998	CD MET	127	59.682	66.115	-17.282	1.00	83.70	A2
ATOM	999	CE MET	127	60.236	65.620	-18.900	1.00	83.23	A2
ATOM	1000	C MET	127	60.847	71.131	-15.599	1.00	82.18	A2
ATOM	1001	OT1 MET	127	60.116	71.958	-16.142	1.00	83.86	A2
ATOM	1002	OT2 MET	127	61.267	71.285	-14.446	1.00	82.04	A2
ATOM	1003	CB MET	138	39.323	80.595	-4.492	1.00	59.39	A3
ATOM	1004	CG MET	138	40.123	79.298	-4.421	1.00	57.97	A3
ATOM	1005	SD MET	138	40.561	78.973	-6.145	1.00	60.85	A3
ATOM	1006	CE MET	138	41.129	77.310	-6.351	1.00	61.48	A3
ATOM	1007	O MET	138	37.021	81.072	-5.454	1.00	60.26	A3
ATOM	1008	C MET	138	36.832	82.262	-5.181	1.00	62.98	A3
ATOM	1009	HT1 MET	138	38.497	82.600	-6.075	1.00	0.00	A3
ATOM	1010	HT2 MET	138	38.313	81.757	-7.329	1.00	0.00	A3
ATOM	1011	N MET	138	38.839	81.784	-6.639	1.00	60.49	A3
ATOM	1012	HT3 MET	138	39.865	81.816	-6.768	1.00	0.00	A3
ATOM	1013	CA MET	138	38.445	80.672	-5.787	1.00	60.51	A3
ATOM	1014	N PRO	139	35.995	80.242	-5.612	1.00	57.82	A3
ATOM	1015	CD PRO	139	36.028	79.060	-6.448	1.00	58.10	A3
ATOM	1016	CA PRO	139	34.654	80.538	-5.142	1.00	54.67	A3
ATOM	1017	CB PRO	139	33.870	79.323	-5.525	1.00	54.54	A3
ATOM	1018	CG PRO	139	34.945	78.290	-5.755	1.00	58.20	A3

FIGURE 5

ATOM	1019 C	PRO	139	34.588	80.0/5	-3.664	1.00	52.24	A3	ATOM	1070 C	PIE	145	26.556	73.938	2.697	1.00	10.55	A3
ATOM	1020 O	PRO	139	35.507	80.623	-2.882	1.00	51.89	A3	ATOM	1071 N	GLN	146	26.745	76.232	2.619	1.00	4.11	A3
ATOM	1021 H	ALA	140	33.499	81.547	-3.342	1.00	49.86	A3	ATOM	1072 H	GLN	146	26.437	77.073	3.015	1.00	0.80	A3
ATOM	1022 H	ALA	140	32.789	81.676	-4.005	1.00	0.00	A3	ATOM	1073 CA	GLN	146	27.660	76.263	1.511	1.00	18.01	A3
ATOM	1023 CA	ALA	140	33.234	81.926	-1.994	1.00	49.39	A3	ATOM	1074 CB	GLN	146	27.907	77.644	1.054	1.00	38.92	A3
ATOM	1024 CB	ALA	140	32.966	83.413	-1.895	1.00	49.94	A3	ATOM	1075 CG	GLN	146	26.884	78.066	0.049	1.00	43.26	A3
ATOM	1025 C	ALA	140	31.978	81.153	-1.590	1.00	49.25	A3	ATOM	1076 CD	GLN	146	27.171	79.440	-0.522	1.00	45.37	A3
ATOM	1026 O	ALA	140	30.889	81.162	-2.205	1.00	49.06	A3	ATOM	1077 OEI	GLN	146	27.851	80.253	0.083	1.00	47.57	A3
ATOM	1027 N	PIE	141	32.293	80.442	-0.506	1.00	47.48	A3	ATOM	1078 NEI	GLN	146	26.689	79.793	-1.692	1.00	47.50	A3
ATOM	1028 H	PIE	141	33.190	80.550	-0.122	1.00	0.00	A3	ATOM	1079 HIE21	GLN	146	26.149	79.149	-2.190	1.00	0.00	A3
ATOM	1029 CA	PIE	141	31.401	79.552	0.208	1.00	45.66	A3	ATOM	1080 HIE22	GLN	146	26.913	80.690	-2.021	1.00	0.00	A3
ATOM	1030 CB	PIE	141	32.215	78.305	0.792	1.00	40.28	A3	ATOM	1081 C	GLN	146	29.005	75.670	1.836	1.00	37.25	A3
ATOM	1031 CG	PIE	141	32.684	77.404	-0.349	1.00	35.35	A3	ATOM	1082 O	GLN	146	29.634	75.093	0.950	1.00	38.38	A3
ATOM	1032 CDI	PIE	141	31.800	76.591	-1.006	1.00	34.39	A3	ATOM	1083 N	ARG	147	29.531	75.775	3.054	1.00	36.37	A3
ATOM	1033 CDI	PIE	141	33.966	77.497	-0.830	1.00	37.69	A3	ATOM	1084 H	ARG	147	29.044	76.300	3.738	1.00	0.00	A3
ATOM	1034 CEI	PIE	141	32.174	75.895	-2.133	1.00	34.00	A3	ATOM	1085 CA	ARG	147	30.798	75.180	3.357	1.00	35.68	A3
ATOM	1035 CEI	PIE	141	34.358	76.807	-1.956	1.00	36.69	A3	ATOM	1086 CB	ARG	147	31.299	75.574	4.713	1.00	37.12	A3
ATOM	1036 CZ	PIE	141	33.449	76.001	-2.614	1.00	37.29	A3	ATOM	1087 CG	ARG	147	32.034	77.016	4.697	1.00	42.68	A3
ATOM	1037 C	PIE	141	31.003	80.580	1.242	1.00	46.54	A3	ATOM	1088 CD	ARG	147	32.634	77.774	5.877	1.00	58.21	A3
ATOM	1038 O	PIE	141	31.584	80.664	2.317	1.00	48.26	A3	ATOM	1089 NE	ARG	147	32.674	78.774	5.877	1.00	58.21	A3
ATOM	1039 N	ALA	142	30.067	81.452	0.843	1.00	47.38	A3	ATOM	1090 HIE	ARG	147	32.475	79.252	5.045	1.00	0.00	A3
ATOM	1040 H	ALA	142	29.624	81.295	-0.020	1.00	0.00	A3	ATOM	1091 CZ	ARG	147	33.519	79.373	6.742	1.00	62.77	A3
ATOM	1041 CA	ALA	142	29.581	82.564	1.668	1.00	46.06	A3	ATOM	1092 HIE1	ARG	147	33.905	78.868	7.936	1.00	61.96	A3
ATOM	1042 CB	ALA	142	28.731	83.546	0.879	1.00	45.04	A3	ATOM	1093 HIE11	ARG	147	34.545	79.379	8.510	1.00	61.00	A3
ATOM	1043 C	ALA	142	28.703	82.132	2.802	1.00	45.27	A3	ATOM	1094 HIE12	ARG	147	33.561	77.980	6.403	1.00	64.80	A3
ATOM	1044 O	ALA	142	28.343	83.002	3.584	1.00	47.38	A3	ATOM	1095 HIE2	ARG	147	33.960	80.584	6.403	1.00	64.80	A3
ATOM	1045 N	SER	143	28.318	80.860	2.899	1.00	43.36	A3	ATOM	1096 HIE21	ARG	147	34.599	81.069	6.999	1.00	0.00	A3
ATOM	1046 H	SER	143	28.724	80.201	2.303	1.00	41.94	A3	ATOM	1097 HIE22	ARG	147	33.665	80.906	5.541	1.00	0.00	A3
ATOM	1047 CA	SER	143	27.377	80.392	3.897	1.00	41.17	A3	ATOM	1098 C	ARG	147	30.570	73.702	3.337	1.00	44.91	A3
ATOM	1048 CB	SER	143	26.036	80.129	3.181	1.00	44.17	A3	ATOM	1099 O	ARG	147	31.233	73.050	2.539	1.00	44.56	A3
ATOM	1049 OG	SER	143	25.323	78.918	3.536	1.00	48.18	A3	ATOM	1100 N	ALA	148	29.544	73.194	4.040	1.00	44.44	A3
ATOM	1050 HG	SER	143	24.455	78.974	3.098	1.00	0.00	A3	ATOM	1101 H	ALA	148	28.926	73.818	4.402	1.00	0.00	A3
ATOM	1051 C	SER	143	27.877	79.145	4.602	1.00	39.79	A3	ATOM	1102 CA	ALA	148	29.358	71.754	4.172	1.00	35.92	A3
ATOM	1052 O	SER	143	28.763	78.452	4.132	1.00	38.50	A3	ATOM	1103 CB	ALA	148	28.217	71.426	5.163	1.00	32.85	A3
ATOM	1053 N	ALA	144	27.218	78.775	5.683	1.00	39.10	A3	ATOM	1104 C	ALA	148	29.077	71.095	2.843	1.00	33.40	A3
ATOM	1054 H	ALA	144	26.449	79.312	5.960	1.00	0.00	A3	ATOM	1105 O	ALA	148	29.765	70.141	2.457	1.00	34.31	A3
ATOM	1055 CA	ALA	144	27.566	77.586	6.411	1.00	39.22	A3	ATOM	1106 N	ALA	149	28.169	71.637	2.077	1.00	32.60	A3
ATOM	1056 CB	ALA	144	26.982	77.598	7.802	1.00	36.97	A3	ATOM	1107 H	ALA	149	27.662	72.424	2.411	1.00	0.00	A3
ATOM	1057 C	ALA	144	26.964	76.420	5.627	1.00	41.58	A3	ATOM	1108 CA	ALA	149	26.595	71.774	0.299	1.00	31.91	A3
ATOM	1058 O	ALA	144	27.206	75.448	5.444	1.00	40.77	A3	ATOM	1109 CB	ALA	149	29.032	71.381	-0.258	1.00	33.75	A3
ATOM	1059 N	PIE	145	25.149	77.203	5.110	1.00	0.00	A3	ATOM	1110 C	ALA	149	29.208	70.661	-1.264	1.00	34.49	A3
ATOM	1060 H	PIE	145	25.307	75.234	4.312	1.00	39.31	A3	ATOM	1111 O	ALA	149	29.867	72.401	-0.052	1.00	33.58	A3
ATOM	1061 CA	PIE	145	23.477	74.452	2.641	1.00	31.91	A3	ATOM	1112 N	GLY	150	29.774	73.035	0.682	1.00	0.00	A3
ATOM	1062 CB	PIE	145	23.477	74.452	2.641	1.00	31.91	A3	ATOM	1113 H	GLY	150	31.017	72.608	-0.913	1.00	31.79	A3
ATOM	1063 CG	PIE	145	23.579	74.900	1.323	1.00	29.02	A3	ATOM	1114 CA	GLY	150	32.113	71.627	-0.478	1.00	31.99	A3
ATOM	1064 CDI	PIE	145	23.013	73.185	2.916	1.00	29.40	A3	ATOM	1115 C	GLY	150	32.997	71.261	-1.265	1.00	31.77	A3
ATOM	1065 CDI	PIE	145	23.225	74.100	0.277	1.00	28.34	A3	ATOM	1116 O	GLY	150	32.075	71.161	0.773	1.00	27.63	A3
ATOM	1066 CEI	PIE	145	22.661	72.389	1.858	1.00	28.80	A3	ATOM	1117 H	GLY	151	31.412	71.524	1.394	1.00	0.00	A3
ATOM	1067 CEI	PIE	145	22.764	72.831	0.549	1.00	30.58	A3	ATOM	1118 H	GLY	151	33.018	70.166	1.243	1.00	32.16	A3
ATOM	1068 CZ	PIE	145	26.266	75.071	3.120	1.00	40.44	A3	ATOM	1119 CA	GLY	151	33.018	70.166	1.243	1.00	32.16	A3
ATOM	1069 C	PIE	145	26.266	75.071	3.120	1.00	40.44	A3	ATOM	1120 C	GLY	151	32.764	68.909	0.409	1.00	33.98	A3

FIGURE 5

ATOM	1223	O	LEU	162	44.107	59.654	-9.070	1.00	36.51	A3	1274	CG1	VAL	168	46.687	60.431	-16.706	1.00	66.78	A3
ATOM	1224	N	GLU	163	41.926	59.589	-9.082	1.00	37.24	A3	1275	CG2	VAL	168	48.278	60.879	-14.840	1.00	68.47	A3
ATOM	1225	H	GLU	163	41.072	60.002	-8.826	1.00	0.00	A3	1276	C	VAL	168	49.579	58.339	-15.469	1.00	66.45	A3
ATOM	1226	CA	GLU	163	41.975	58.327	-9.771	1.00	40.47	A3	1277	O	VAL	168	50.458	58.183	-16.302	1.00	66.22	A3
ATOM	1227	CB	GLU	163	40.566	57.716	-9.835	1.00	45.38	A3	1278	N	LEU	169	49.823	58.241	-14.177	1.00	68.83	A3
ATOM	1228	CG	GLU	163	40.264	56.975	-8.126	1.00	51.84	A3	1279	H	LEU	169	49.102	58.404	-13.536	1.00	0.00	A3
ATOM	1229	CD	GLU	163	41.291	55.889	-8.126	1.00	57.97	A3	1280	CA	LEU	169	51.141	57.899	-13.695	1.00	71.81	A3
ATOM	1230	OE1	GLU	163	40.897	54.722	-8.092	1.00	62.01	A3	1281	CB	LEU	169	51.249	58.228	-12.188	1.00	71.53	A3
ATOM	1231	OE2	GLU	163	42.466	56.180	-7.832	1.00	59.17	A3	1282	C	LEU	169	51.137	59.732	-11.813	1.00	70.68	A3
ATOM	1232	O	GLU	163	42.586	58.430	-11.142	1.00	41.34	A3	1283	CD1	LEU	169	51.187	59.826	-10.298	1.00	69.39	A3
ATOM	1233	N	GLU	163	43.456	57.633	-11.486	1.00	42.17	A3	1284	CD2	LEU	169	52.223	60.580	-12.491	1.00	68.49	A3
ATOM	1234	O	VAL	164	42.257	59.436	-11.920	1.00	42.28	A3	1285	C	LEU	169	51.333	56.414	-13.979	1.00	73.61	A3
ATOM	1235	H	VAL	164	41.589	60.091	-11.615	1.00	0.00	A3	1286	O	LEU	169	52.408	56.013	-14.429	1.00	74.75	A3
ATOM	1236	CA	VAL	164	42.911	59.609	-13.187	1.00	44.13	A3	1287	N	ARG	170	50.309	55.583	-13.819	1.00	75.45	A3
ATOM	1237	CB	VAL	164	42.207	60.711	-13.940	1.00	45.52	A3	1288	H	ARG	170	49.488	55.923	-13.399	1.00	0.00	A3
ATOM	1238	CG1	VAL	164	42.892	60.975	-15.278	1.00	48.79	A3	1289	CA	ARG	170	50.364	54.179	-14.199	1.00	78.17	A3
ATOM	1239	CG2	VAL	164	40.786	60.269	-14.226	1.00	46.09	A3	1290	CB	ARG	170	48.944	53.642	-14.004	1.00	78.45	A3
ATOM	1240	C	VAL	164	44.386	59.933	-12.991	1.00	46.13	A3	1291	CG	ARG	170	48.394	52.506	-14.871	1.00	78.17	A3
ATOM	1241	O	VAL	164	45.192	59.473	-13.794	1.00	45.99	A3	1292	CD	ARG	170	48.744	51.181	-14.271	1.00	77.25	A3
ATOM	1242	N	SER	165	44.879	60.677	-12.006	1.00	49.51	A3	1293	NE	ARG	170	48.123	51.120	-12.970	1.00	76.15	A3
ATOM	1243	H	SER	165	44.287	61.173	-11.396	1.00	0.00	A3	1294	HE	ARG	170	47.245	51.528	-12.824	1.00	0.00	A3
ATOM	1244	CA	SER	165	46.325	60.845	-11.895	1.00	53.44	A3	1295	CZ	ARG	170	48.758	50.547	-11.970	1.00	76.14	A3
ATOM	1245	CB	SER	165	46.715	61.796	-10.775	1.00	54.77	A3	1296	NH1	ARG	170	49.973	50.017	-12.112	1.00	76.84	A3
ATOM	1246	CG	SER	165	46.049	61.618	-9.530	1.00	59.99	A3	1297	NH11	ARG	170	50.441	50.030	-12.994	1.00	0.00	A3
ATOM	1247	HC	SER	165	45.997	60.694	-9.261	1.00	0.00	A3	1298	NH12	ARG	170	50.406	49.570	-11.329	1.00	0.00	A3
ATOM	1248	C	SER	165	46.958	59.302	-11.630	1.00	55.15	A3	1299	NH2	ARG	170	48.147	50.492	-10.806	1.00	77.02	A3
ATOM	1249	O	SER	165	48.028	59.227	-12.148	1.00	55.02	A3	1300	NH21	ARG	170	47.237	50.890	-10.714	1.00	0.00	A3
ATOM	1250	N	TYR	166	45.374	58.948	-10.549	1.00	0.00	A3	1301	NH22	ARG	170	48.586	50.052	-10.023	1.00	0.00	A3
ATOM	1251	H	TYR	166	45.374	58.948	-10.549	1.00	0.00	A3	1302	C	ARG	170	50.870	54.052	-15.647	1.00	79.84	A3
ATOM	1252	CA	TYR	166	46.617	57.273	-10.625	1.00	61.42	A3	1303	O	ARG	170	51.924	53.470	-15.908	1.00	80.07	A3
ATOM	1253	CB	TYR	166	45.543	56.653	-9.680	1.00	64.05	A3	1304	N	HIS	171	50.193	54.663	-16.611	1.00	81.38	A3
ATOM	1254	CG	TYR	166	45.502	55.138	-9.682	1.00	69.00	A3	1305	H	HIS	171	49.433	55.234	-16.359	1.00	0.00	A3
ATOM	1255	CD1	TYR	166	44.389	54.501	-10.185	1.00	71.64	A3	1306	CA	HIS	171	50.663	54.597	-17.970	1.00	84.03	A3
ATOM	1256	CE1	TYR	166	44.367	53.130	-10.283	1.00	73.15	A3	1307	CB	HIS	171	49.590	55.054	-18.902	1.00	86.82	A3
ATOM	1257	CD2	TYR	166	46.594	54.409	-9.257	1.00	71.27	A3	1308	CG	HIS	171	48.496	54.037	-19.147	1.00	90.23	A3
ATOM	1258	CZ	TYR	166	46.584	53.040	-9.346	1.00	72.92	A3	1309	CD2	HIS	171	47.467	53.765	-18.272	1.00	91.55	A3
ATOM	1259	CH	TYR	166	45.468	52.417	-9.862	1.00	75.71	A3	1310	ND1	HIS	171	48.308	53.301	-20.248	1.00	92.24	A3
ATOM	1260	OH	TYR	166	45.474	51.038	-10.016	1.00	80.61	A3	1311	HD1	HIS	171	48.887	53.287	-21.044	1.00	0.00	A3
ATOM	1261	NH	TYR	166	44.571	50.736	-10.134	1.00	0.00	A3	1312	CE1	HIS	171	47.204	52.605	-20.077	1.00	92.41	A3
ATOM	1262	C	TYR	166	46.712	56.567	-11.987	1.00	62.34	A3	1313	NE2	HIS	171	46.711	52.892	-18.891	1.00	92.59	A3
ATOM	1263	O	TYR	166	47.766	55.981	-12.282	1.00	63.25	A3	1314	HE2	HIS	171	45.884	52.511	-18.518	1.00	0.00	A3
ATOM	1264	N	ALA	167	45.727	56.622	-12.884	1.00	61.27	A3	1315	C	HIS	171	51.907	55.446	-18.232	1.00	85.42	A3
ATOM	1265	H	ALA	167	44.893	57.089	-12.678	1.00	0.00	A3	1316	O	HIS	171	52.440	55.352	-19.344	1.00	85.98	A3
ATOM	1266	CA	ALA	167	45.933	55.982	-14.159	1.00	61.47	A3	1317	N	LEU	172	52.359	56.307	-17.302	1.00	86.13	A3
ATOM	1267	CB	ALA	167	44.608	55.904	-14.904	1.00	60.98	A3	1318	H	LEU	172	51.870	56.411	-16.463	1.00	0.00	A3
ATOM	1268	C	ALA	167	46.982	56.694	-15.020	1.00	62.19	A3	1319	CA	LEU	172	53.550	57.133	-17.496	1.00	86.02	A3
ATOM	1269	O	ALA	167	47.719	56.000	-15.734	1.00	62.63	A3	1320	CB	LEU	172	53.500	58.357	-16.607	1.00	86.31	A3
ATOM	1270	N	VAL	168	47.210	58.011	-14.991	1.00	63.37	A3	1321	CG	LEU	172	54.022	59.658	-17.203	1.00	87.48	A3
ATOM	1271	H	VAL	168	46.756	58.570	-14.330	1.00	0.00	A3	1322	CD1	LEU	172	53.436	59.939	-18.596	1.00	87.68	A3
ATOM	1272	CA	VAL	168	48.174	58.593	-15.923	1.00	65.62	A3	1323	CD2	LEU	172	53.645	60.778	-16.251	1.00	87.95	A3
ATOM	1273	CB	VAL	168	48.061	60.121	-16.131	1.00	66.30	A3	1324	C	LEU	172	54.815	56.357	-17.180	1.00	85.92	A3

FIGURE 5

ATOM 2345	CD1 PHE	341	23.510	16.923	17.359	1.00	43.44	B3
ATOM 2346	CD1 PHE	341	25.527	16.175	18.388	1.00	47.03	B3
ATOM 2347	CE1 PHE	341	23.812	18.172	17.831	1.00	49.15	B3
ATOM 2348	CE2 PHE	341	25.827	17.426	18.862	1.00	47.86	B3
ATOM 2349	CZ PHE	341	24.952	18.437	18.580	1.00	48.36	B3
ATOM 2350	C PHE	341	22.684	12.510	17.672	1.00	49.56	B3
ATOM 2351	O PHE	341	23.309	11.938	16.781	1.00	51.46	B3
ATOM 2352	H ALA	342	21.625	11.985	18.245	1.00	47.40	B3
ATOM 2353	H ALA	342	21.026	12.585	18.741	1.00	0.00	B3
ATOM 2354	CA ALA	342	21.167	10.650	17.997	1.00	46.11	B3
ATOM 2355	CB ALA	342	19.874	10.531	18.804	1.00	47.10	B3
ATOM 2356	C ALA	342	20.962	10.149	16.556	1.00	44.37	B3
ATOM 2357	O SER	343	20.138	9.247	16.418	1.00	45.65	B3
ATOM 2358	N SER	343	21.537	10.573	15.423	1.00	41.37	B3
ATOM 2359	H SER	343	22.191	11.301	15.428	1.00	0.00	B3
ATOM 2360	CA SER	343	21.274	9.923	14.145	1.00	38.80	B3
ATOM 2361	CB SER	343	19.842	10.138	13.636	1.00	38.79	B3
ATOM 2362	CG SER	343	19.205	11.300	14.182	1.00	37.75	B3
ATOM 2363	HG SER	343	18.963	11.059	15.092	1.00	0.00	B3
ATOM 2364	C SER	343	22.172	10.467	13.088	1.00	38.22	B3
ATOM 2365	O SER	343	22.810	11.471	13.382	1.00	38.30	B3
ATOM 2366	N ALA	344	22.206	9.845	11.888	1.00	36.73	B3
ATOM 2367	H ALA	344	21.762	8.978	11.805	1.00	0.00	B3
ATOM 2368	CA ALA	344	22.914	10.384	10.715	1.00	38.09	B3
ATOM 2369	CB ALA	344	22.583	9.640	9.422	1.00	36.78	B3
ATOM 2370	C ALA	344	22.472	11.842	10.496	1.00	37.72	B3
ATOM 2371	O ALA	344	23.271	12.765	10.676	1.00	38.42	B3
ATOM 2372	N PHE	345	21.194	12.042	10.163	1.00	36.10	B3
ATOM 2373	H PHE	345	20.668	11.298	9.811	1.00	0.00	B3
ATOM 2374	CA PHE	345	20.564	13.338	10.195	1.00	34.69	B3
ATOM 2375	CB PHE	345	19.040	13.254	10.128	1.00	33.24	B3
ATOM 2376	CG PHE	345	18.462	14.656	9.918	1.00	31.72	B3
ATOM 2377	CD1 PHE	345	17.715	15.223	10.905	1.00	26.64	B3
ATOM 2378	CD2 PHE	345	18.767	15.343	8.745	1.00	29.99	B3
ATOM 2379	CE1 PHE	345	17.284	16.503	10.682	1.00	33.56	B3
ATOM 2380	CE2 PHE	345	18.333	16.619	8.537	1.00	30.81	B3
ATOM 2381	CZ PHE	345	17.581	17.201	9.520	1.00	31.44	B3
ATOM 2382	C PHE	345	20.888	14.145	11.458	1.00	35.02	B3
ATOM 2383	O PHE	345	21.246	15.319	11.292	1.00	37.81	B3
ATOM 2384	N GLN	346	20.814	13.688	12.691	1.00	33.53	B3
ATOM 2385	H GLN	346	20.516	12.778	12.894	1.00	0.00	B3
ATOM 2386	CA GLN	346	21.156	14.586	13.758	1.00	33.46	B3
ATOM 2387	CB GLN	346	20.899	13.985	15.061	1.00	33.80	B3
ATOM 2388	CG GLN	346	19.459	14.284	15.174	1.00	35.68	B3
ATOM 2389	CD GLN	346	18.788	13.658	16.344	1.00	38.48	B3
ATOM 2390	OE1 GLN	346	19.358	13.328	17.374	1.00	41.78	B3
ATOM 2391	OE2 GLN	346	17.508	13.463	16.167	1.00	41.08	B3
ATOM 2392	HE2 GLN	346	17.088	13.724	15.323	1.00	0.00	B3
ATOM 2393	HE2 GLN	346	17.026	13.063	16.919	1.00	0.00	B3
ATOM 2394	C GLN	346	22.564	15.051	13.773	1.00	35.73	B3
ATOM 2395	O GLN	346	22.766	16.231	14.051	1.00	38.18	B3
ATOM 2396	N ARG	347	23.507	14.190	13.431	1.00	35.57	B3
ATOM 2397	H ARG	347	23.248	13.289	13.157	1.00	0.00	B3
ATOM 2398	CA ARG	347	24.907	14.538	13.396	1.00	35.95	B3
ATOM 2399	CB ARG	347	25.760	12.236	13.222	1.00	36.20	B3
ATOM 2400	CD ARG	347	26.198	12.549	14.540	1.00	37.41	B3
ATOM 2401	CG ARG	347	26.986	11.246	14.373	1.00	39.70	B3
ATOM 2402	NE ARG	347	26.072	10.167	14.028	1.00	47.18	B3
ATOM 2403	HE ARG	347	25.416	9.893	14.701	1.00	0.00	B3
ATOM 2404	CZ ARG	347	26.071	9.516	12.846	1.00	48.49	B3
ATOM 2405	NH1 ARG	347	26.938	9.802	11.882	1.00	50.22	B3
ATOM 2406	NH11 ARG	347	27.602	10.528	12.031	1.00	0.00	B3
ATOM 2407	NH12 ARG	347	26.905	9.314	11.011	1.00	0.00	B3
ATOM 2408	NH2 ARG	347	25.130	8.608	12.574	1.00	48.40	B3
ATOM 2409	NH21 ARG	347	24.423	8.408	13.252	1.00	0.00	B3
ATOM 2410	NH22 ARG	347	25.126	8.131	11.697	1.00	0.00	B3
ATOM 2411	C ARG	347	25.183	15.544	12.267	1.00	35.54	B3
ATOM 2412	O ARG	347	25.077	16.549	12.445	1.00	36.74	B3
ATOM 2413	N ARG	348	24.611	15.353	11.096	1.00	34.74	B3
ATOM 2414	H ARG	348	24.043	14.559	11.005	1.00	0.00	B3
ATOM 2415	CA ARG	348	24.802	16.225	9.954	1.00	35.24	B3
ATOM 2416	CB ARG	348	24.091	15.623	8.751	1.00	36.76	B3
ATOM 2417	CG ARG	348	24.778	14.303	8.450	1.00	44.22	B3
ATOM 2418	CD ARG	348	24.014	13.379	7.529	1.00	49.23	B3
ATOM 2419	NE ARG	348	24.705	12.090	7.457	1.00	54.27	B3
ATOM 2420	HE ARG	348	25.300	11.836	8.193	1.00	0.00	B3
ATOM 2421	CZ ARG	348	24.557	11.226	6.430	1.00	53.75	B3
ATOM 2422	NH1 ARG	348	23.758	11.479	5.381	1.00	51.85	B3
ATOM 2423	NH11 ARG	348	23.234	12.329	5.339	1.00	0.00	B3
ATOM 2424	NH12 ARG	348	23.680	10.807	4.645	1.00	0.00	B3
ATOM 2425	NH2 ARG	348	25.252	10.083	6.462	1.00	54.51	B3
ATOM 2426	NH21 ARG	348	25.169	9.424	5.714	1.00	0.00	B3
ATOM 2427	NH22 ARG	348	25.860	9.894	7.232	1.00	0.00	B3
ATOM 2428	C ARG	348	24.283	17.629	10.237	1.00	34.80	B3
ATOM 2429	O ARG	348	25.078	18.564	10.219	1.00	35.16	B3
ATOM 2430	N ALA	349	23.008	17.795	10.607	1.00	33.85	B3
ATOM 2431	H ALA	349	22.470	16.984	10.755	1.00	0.00	B3
ATOM 2432	CA ALA	349	22.352	19.083	10.853	1.00	32.96	B3
ATOM 2433	CB ALA	349	20.809	18.894	11.070	1.00	33.46	B3
ATOM 2434	C ALA	349	22.945	19.746	12.083	1.00	31.84	B3
ATOM 2435	O ALA	349	22.981	20.969	12.210	1.00	30.69	B3
ATOM 2436	N GLY	350	23.444	18.954	13.018	1.00	31.30	B3
ATOM 2437	H GLY	350	23.308	17.984	12.976	1.00	0.00	B3
ATOM 2438	CA GLY	350	24.117	19.505	14.181	1.00	31.08	B3
ATOM 2439	CB GLY	350	25.462	20.025	13.753	1.00	30.79	B3
ATOM 2440	O GLY	350	25.974	21.010	14.280	1.00	31.38	B3
ATOM 2441	N GLY	351	25.991	19.374	12.731	1.00	30.03	B3
ATOM 2442	H GLY	351	25.546	18.582	12.367	1.00	0.00	B3
ATOM 2443	CA GLY	351	27.263	19.735	12.184	1.00	29.95	B3
ATOM 2444	C GLY	351	27.182	21.097	11.534	1.00	29.25	B3
ATOM 2445	O GLY	351	27.937	21.974	11.919	1.00	28.73	B3
ATOM 2446	N VAL	352	26.336	21.285	10.522	1.00	28.92	B3

FIGURE 5

ATOM 2447 H VAL 352	25.859	20.484	10.214	1.00	0.00	B3
ATOM 2448 CA VAL 352	26.079	22.567	9.881	1.00	28.59	B3
ATOM 2449 CB VAL 352	24.845	22.452	9.004	1.00	28.96	B3
ATOM 2450 CG VAL 352	24.627	23.785	8.346	1.00	30.86	B3
ATOM 2451 CG2 VAL 352	25.021	21.475	7.875	1.00	26.94	B3
ATOM 2452 C VAL 352	25.849	23.709	10.890	1.00	29.29	B3
ATOM 2453 O VAL 352	26.520	24.747	10.853	1.00	31.02	B3
ATOM 2454 N LBU 353	24.923	23.543	11.819	1.00	27.52	B3
ATOM 2455 H LBU 353	24.404	22.709	11.838	1.00	0.00	B3
ATOM 2456 CA LBU 353	24.635	24.548	12.817	1.00	26.18	B3
ATOM 2457 CB LBU 353	23.434	24.113	13.636	1.00	27.87	B3
ATOM 2458 CG LBU 353	22.098	24.034	12.931	1.00	26.54	B3
ATOM 2459 CD1 LBU 353	21.064	23.617	13.924	1.00	25.49	B3
ATOM 2460 CD2 LBU 353	21.750	25.372	12.320	1.00	28.23	B3
ATOM 2461 C LBU 353	25.742	24.905	13.772	1.00	27.17	B3
ATOM 2462 O LBU 353	25.838	26.093	14.088	1.00	28.00	B3
ATOM 2463 N VAL 354	26.539	23.949	14.318	1.00	27.20	B3
ATOM 2464 H VAL 354	26.321	23.006	14.139	1.00	0.00	B3
ATOM 2465 CA VAL 354	27.712	24.212	15.157	1.00	24.62	B3
ATOM 2466 CB VAL 354	28.236	22.910	15.745	1.00	22.01	B3
ATOM 2467 CG1 VAL 354	29.568	23.089	16.406	1.00	19.82	B3
ATOM 2468 CG2 VAL 354	27.276	22.467	16.802	1.00	23.96	B3
ATOM 2469 C VAL 354	28.812	24.893	14.332	1.00	25.46	B3
ATOM 2470 O VAL 354	29.439	25.832	14.798	1.00	26.23	B3
ATOM 2471 N VAL 355	29.059	24.530	13.089	1.00	26.12	B3
ATOM 2472 H ALA 355	28.579	23.745	12.744	1.00	0.00	B3
ATOM 2473 CA ALA 355	30.034	24.591	10.869	1.00	22.08	B3
ATOM 2474 CB ALA 355	30.315	27.498	12.344	1.00	31.93	B3
ATOM 2475 C ALA 355	28.271	26.484	11.802	1.00	30.30	B3
ATOM 2476 O ALA 355	27.654	26.134	11.465	1.00	0.00	B3
ATOM 2477 N SER 356	26.401	28.147	11.016	1.00	35.23	B3
ATOM 2478 H SER 356	25.679	29.380	10.905	1.00	43.82	B3
ATOM 2479 CA SER 356	26.250	30.004	10.429	1.00	0.00	B3
ATOM 2480 CB SER 356	27.763	29.098	12.901	1.00	29.75	B3
ATOM 2481 CG SER 356	28.115	30.289	12.898	1.00	28.35	B3
ATOM 2482 C SER 356	27.465	28.464	14.015	1.00	27.82	B3
ATOM 2483 O SER 356	27.301	27.498	14.019	1.00	0.00	B3
ATOM 2484 N HIS 357	27.434	29.194	15.259	1.00	26.58	B3
ATOM 2485 H HIS 357	26.735	28.365	16.305	1.00	25.77	B3
ATOM 2486 CA HIS 357	25.219	28.360	16.063	1.00	27.67	B3
ATOM 2487 CB HIS 357	24.563	28.767	14.915	1.00	28.94	B3
ATOM 2488 CG HIS 357	24.277	27.963	16.915	1.00	28.43	B3
ATOM 2489 CD1 HIS 357	24.456	27.622	17.828	1.00	0.00	B3
ATOM 2490 CD2 HIS 357	23.112	28.103	16.337	1.00	28.64	B3
ATOM 2491 ND1 HIS 357	23.298	28.589	15.130	1.00	29.48	B3
ATOM 2492 CE1 HIS 357	22.576	28.801	14.495	1.00	27.93	B3
ATOM 2493 NE2 HIS 357	28.852	29.506	15.645	1.00	0.00	B3
ATOM 2494 IE2 HIS 357	29.119	30.606	16.115	1.00	29.15	B3
ATOM 2497 O HIS 357						B3
ATOM 2498 N LBU 358	29.830	28.637	15.383	1.00	28.33	B3
ATOM 2499 H LBU 358	29.624	27.761	14.987	1.00	0.00	B3
ATOM 2500 CA LBU 358	31.211	28.940	15.721	1.00	26.39	B3
ATOM 2501 CB LBU 358	32.030	27.702	15.547	1.00	21.42	B3
ATOM 2502 CG LBU 358	33.457	27.878	15.734	1.00	20.42	B3
ATOM 2503 CD1 LBU 358	33.805	28.078	17.165	1.00	16.79	B3
ATOM 2504 CD2 LBU 358	34.075	26.714	15.072	1.00	22.89	B3
ATOM 2505 C LBU 358	31.721	30.067	14.822	1.00	26.45	B3
ATOM 2506 O LBU 358	32.372	30.939	15.378	1.00	27.12	B3
ATOM 2507 N GLN 359	31.460	30.130	13.518	1.00	26.41	B3
ATOM 2508 H GLN 359	31.048	29.337	13.114	1.00	0.00	B3
ATOM 2509 CA GLN 359	31.863	31.254	12.671	1.00	29.10	B3
ATOM 2510 CB GLN 359	31.204	31.209	11.292	1.00	30.49	B3
ATOM 2511 CG GLN 359	31.395	29.952	10.455	1.00	38.94	B3
ATOM 2512 CD GLN 359	32.842	29.636	10.091	1.00	42.09	B3
ATOM 2513 OE1 GLN 359	32.774	29.979	10.821	1.00	46.15	B3
ATOM 2514 NE2 GLN 359	33.103	28.987	8.967	1.00	41.34	B3
ATOM 2515 IE2 GLN 359	32.341	28.706	8.412	1.00	0.00	B3
ATOM 2516 IE22 GLN 359	34.039	28.838	8.740	1.00	0.00	B3
ATOM 2517 C GLN 359	31.512	32.621	13.254	1.00	29.39	B3
ATOM 2518 O GLN 359	32.427	33.427	13.484	1.00	30.06	B3
ATOM 2519 N SER 360	30.201	32.810	13.528	1.00	28.66	B3
ATOM 2520 H SER 360	29.595	32.063	13.343	1.00	0.00	B3
ATOM 2521 CA SER 360	29.570	34.003	14.071	1.00	27.31	B3
ATOM 2522 CB SER 360	28.121	33.761	14.336	1.00	26.70	B3
ATOM 2523 CG SER 360	27.493	33.539	13.078	1.00	29.72	B3
ATOM 2524 HG SER 360	26.637	33.112	13.288	1.00	0.00	B3
ATOM 2525 C SER 360	30.202	34.287	15.353	1.00	27.15	B3
ATOM 2526 O SER 360	30.575	35.550	15.498	1.00	26.43	B3
ATOM 2527 N PHE 361	30.383	33.403	16.246	1.00	25.38	B3
ATOM 2528 H PHE 361	30.055	32.499	16.040	1.00	0.00	B3
ATOM 2529 CA PHE 361	31.092	32.626	17.517	1.00	25.20	B3
ATOM 2530 CB PHE 361	31.092	32.335	18.302	1.00	23.30	B3
ATOM 2531 CG PHE 361	31.796	32.394	19.655	1.00	23.63	B3
ATOM 2532 CD1 PHE 361	31.127	32.854	20.777	1.00	22.44	B3
ATOM 2533 CD2 PHE 361	33.098	31.931	19.770	1.00	23.35	B3
ATOM 2534 CE1 PHE 361	33.772	32.834	22.000	1.00	22.78	B3
ATOM 2535 CE2 PHE 361	33.719	31.921	21.002	1.00	21.26	B3
ATOM 2536 CZ PHE 361	33.058	32.368	22.114	1.00	19.54	B3
ATOM 2537 C PHE 361	32.505	34.143	17.305	1.00	26.56	B3
ATOM 2538 O PHE 361	32.914	34.979	18.103	1.00	26.76	B3
ATOM 2539 N LBU 362	33.309	33.645	18.441	1.00	28.17	B3
ATOM 2540 H LBU 362	32.962	32.921	15.874	1.00	0.00	B3
ATOM 2541 CA LBU 362	34.679	34.089	16.222	1.00	28.89	B3
ATOM 2542 CB LBU 362	35.452	33.125	15.338	1.00	28.18	B3
ATOM 2543 CG LBU 362	35.603	31.656	15.781	1.00	29.61	B3
ATOM 2544 CD1 LBU 362	36.306	30.996	14.633	1.00	31.63	B3
ATOM 2545 CD2 LBU 362	36.374	31.433	17.055	1.00	26.38	B3
ATOM 2546 C LBU 362	34.692	35.449	15.536	1.00	29.18	B3
ATOM 2547 O LBU 362	35.649	36.202	15.748	1.00	27.43	B3
ATOM 2548 N GLU 363	33.664	35.763	14.710	1.00	29.54	B3

FIGURES

ATOM 2753	CG LEU 419	32.866	5.453	-1.244	1.00	39.61	C1
ATOM 2754	CD1 LEU 419	31.866	54.918	-1.609	1.00	39.24	C1
ATOM 2755	CD2 LEU 419	34.349	53.207	-2.553	1.00	40.02	C1
ATOM 2756	C LEU 419	36.102	54.041	1.047	1.00	32.33	C1
ATOM 2757	O LEU 419	37.198	53.973	0.549	1.00	31.60	C1
ATOM 2758	N GLU 420	35.974	54.483	2.273	1.00	31.92	C1
ATOM 2759	H GLU 420	35.068	54.528	2.648	1.00	0.00	C1
ATOM 2760	CA GLU 420	37.078	54.905	3.092	1.00	31.79	C1
ATOM 2761	CB GLU 420	36.477	55.462	4.344	1.00	34.29	C1
ATOM 2762	CG GLU 420	37.430	56.240	5.185	1.00	38.66	C1
ATOM 2763	CD GLU 420	36.952	56.499	6.609	1.00	45.20	C1
ATOM 2764	OE1 GLU 420	37.873	56.849	7.367	1.00	45.67	C1
ATOM 2765	OE2 GLU 420	35.745	56.345	6.954	1.00	44.21	C1
ATOM 2766	C GLU 420	38.043	53.763	3.423	1.00	31.87	C1
ATOM 2767	O GLU 420	39.233	53.949	3.270	1.00	32.82	C1
ATOM 2768	N GLN 421	37.533	52.824	3.954	1.00	30.46	C1
ATOM 2769	H GLN 421	36.583	52.556	4.098	1.00	0.00	C1
ATOM 2770	CA GLN 421	38.366	51.461	4.283	1.00	29.34	C1
ATOM 2771	CB GLN 421	37.545	50.389	4.984	1.00	30.48	C1
ATOM 2772	CG GLN 421	37.308	50.634	6.463	1.00	33.58	C1
ATOM 2773	CD GLN 421	36.320	49.623	7.058	1.00	37.89	C1
ATOM 2774	OE1 GLN 421	35.357	49.236	6.398	1.00	43.18	C1
ATOM 2775	OE2 GLN 421	36.427	49.093	8.275	1.00	37.13	C1
ATOM 2776	HE21 GLN 421	35.695	48.505	8.556	1.00	0.00	C1
ATOM 2777	HE22 GLN 421	37.207	49.330	8.812	1.00	0.00	C1
ATOM 2778	C GLN 421	38.991	50.862	3.026	1.00	27.36	C1
ATOM 2779	O GLN 421	40.132	50.445	3.099	1.00	25.09	C1
ATOM 2780	N VAL 422	38.379	50.845	1.847	1.00	23.57	C1
ATOM 2781	H VAL 422	37.448	51.138	1.803	1.00	0.00	C1
ATOM 2782	CA VAL 422	39.077	50.420	0.651	1.00	23.52	C1
ATOM 2783	CB VAL 422	38.163	50.636	-0.556	1.00	22.67	C1
ATOM 2784	CG1 VAL 422	38.873	50.435	-1.868	1.00	21.56	C1
ATOM 2785	CG2 VAL 422	37.057	49.610	-0.465	1.00	26.79	C1
ATOM 2786	C VAL 422	40.353	51.254	0.514	1.00	26.22	C1
ATOM 2787	O VAL 422	41.458	50.708	0.508	1.00	24.77	C1
ATOM 2788	N ARG 423	40.275	52.599	0.575	1.00	27.49	C1
ATOM 2789	H ARG 423	39.402	53.016	0.735	1.00	0.00	C1
ATOM 2790	CA ARG 423	41.436	53.456	0.346	1.00	25.91	C1
ATOM 2791	CB ARG 423	40.167	53.366	-0.807	1.00	22.81	C1
ATOM 2792	CG ARG 423	40.525	54.798	-2.172	1.00	25.55	C1
ATOM 2793	CD ARG 423	39.707	55.387	-3.216	1.00	25.38	C1
ATOM 2794	NE ARG 423	39.168	56.173	-2.989	1.00	0.00	C1
ATOM 2795	HE ARG 423	39.639	54.928	-4.466	1.00	27.32	C1
ATOM 2796	C2 ARG 423	40.264	53.857	-4.949	1.00	26.37	C1
ATOM 2797	NH1 ARG 423	40.884	53.341	-4.365	1.00	0.00	C1
ATOM 2798	NH11 ARG 423	40.150	53.595	-5.907	1.00	0.00	C1
ATOM 2799	NH12 ARG 423	38.960	55.682	-5.325	1.00	30.38	C1
ATOM 2800	NH2 ARG 423	38.539	56.537	-5.023	1.00	0.00	C1
ATOM 2801	NH22 ARG 423	38.865	55.385	-6.275	1.00	0.00	C1
ATOM 2803	C ARG 423	42.429	53.241	1.432	1.00	23.60	C1
ATOM 2804	J ARG 423						
ATOM 2805	N LYS 424	43.594	53.147	1.127	1.00	24.37	C1
ATOM 2806	H LYS 424	42.065	53.050	2.668	1.00	24.38	C1
ATOM 2807	CA LYS 424	41.109	53.051	2.890	1.00	0.00	C1
ATOM 2808	CB LYS 424	43.043	52.855	3.722	1.00	25.12	C1
ATOM 2809	CG LYS 424	42.352	52.791	5.051	1.00	23.89	C1
ATOM 2810	CD LYS 424	43.312	52.936	6.190	1.00	28.56	C1
ATOM 2811	CE LYS 424	42.579	52.580	7.486	1.00	35.51	C1
ATOM 2812	NZ LYS 424	41.338	53.425	7.853	1.00	40.33	C1
ATOM 2813	H21 LYS 424	40.519	52.722	8.834	1.00	42.23	C1
ATOM 2814	H22 LYS 424	41.079	52.559	9.695	1.00	0.00	C1
ATOM 2815	H23 LYS 424	40.208	51.814	8.435	1.00	0.00	C1
ATOM 2816	C LYS 424	39.689	53.306	9.065	1.00	0.00	C1
ATOM 2817	O LYS 424	44.761	51.547	3.462	1.00	27.10	C1
ATOM 2818	N ILE 425	44.923	51.425	3.848	1.00	30.64	C1
ATOM 2819	H ILE 425	43.190	50.542	2.794	1.00	26.83	C1
ATOM 2820	CA ILE 425	42.260	50.607	2.488	1.00	0.00	C1
ATOM 2821	CB ILE 425	43.949	49.312	2.561	1.00	25.46	C1
ATOM 2822	CG2 ILE 425	42.965	48.093	2.336	1.00	24.91	C1
ATOM 2823	CG1 ILE 425	43.654	46.786	1.995	1.00	22.01	C1
ATOM 2824	CD ILE 425	42.229	47.909	3.633	1.00	25.34	C1
ATOM 2825	C ILE 425	40.885	47.169	3.422	1.00	25.68	C1
ATOM 2826	O ILE 425	44.824	49.549	1.346	1.00	23.84	C1
ATOM 2827	N GLN 426	45.959	49.069	1.316	1.00	24.57	C1
ATOM 2828	H GLN 426	44.361	50.267	0.323	1.00	23.28	C1
ATOM 2829	CA GLN 426	43.451	50.630	0.393	1.00	0.00	C1
ATOM 2830	CB GLN 426	45.164	50.531	-0.871	1.00	24.13	C1
ATOM 2831	CG GLN 426	44.421	51.344	-1.896	1.00	24.04	C1
ATOM 2832	CD GLN 426	43.275	50.539	-2.396	1.00	23.56	C1
ATOM 2833	OE1 GLN 426	42.446	51.105	-3.511	1.00	23.92	C1
ATOM 2834	OE2 GLN 426	41.704	52.047	-3.345	1.00	25.34	C1
ATOM 2835	HE21 GLN 426	42.337	50.509	-4.672	1.00	27.55	C1
ATOM 2836	HE22 GLN 426	41.755	50.948	-5.323	1.00	0.00	C1
ATOM 2837	C GLN 426	42.850	49.696	-4.851	1.00	0.00	C1
ATOM 2838	O GLN 426	46.404	51.312	-0.488	1.00	26.69	C1
ATOM 2839	N GLY 427	47.486	51.109	-1.046	1.00	29.73	C1
ATOM 2840	H GLY 427	46.300	52.204	0.499	1.00	76.49	C1
ATOM 2841	CA GLY 427	45.410	52.414	0.854	1.00	0.00	C1
ATOM 2842	C GLY 427	47.446	52.894	1.022	1.00	24.25	C1
ATOM 2843	O GLY 427	48.467	51.913	1.589	1.00	23.08	C1
ATOM 2844	N ASP 428	49.597	51.921	1.106	1.00	22.78	C1
ATOM 2845	H ASP 428	48.107	51.073	2.575	1.00	22.75	C1
ATOM 2846	CA ASP 428	47.189	51.111	2.918	1.00	0.00	C1
ATOM 2847	CB ASP 428	49.039	50.108	3.131	1.00	23.87	C1
ATOM 2848	CG ASP 428	48.415	49.199	4.117	1.00	26.52	C1
ATOM 2849	OD1 ASP 428	47.437	49.779	5.097	1.00	28.84	C1
ATOM 2850	OD2 ASP 428	46.420	49.151	5.265	1.00	31.81	C1
ATOM 2851	C ASP 428	49.626	49.191	2.063	1.00	24.16	C1
ATOM 2852	O ASP 428	50.812	48.896	2.088	1.00	26.17	C1
ATOM 2853	N GLY 429	48.840	48.822	1.069	1.00	23.01	C1
ATOM 2854	H GLY 429	47.905	49.113	1.071	1.00	0.00	C1

Summary

ATOM	2855	CA	GLY	429	49.289	~.964	0.079	1.00	25.44	CI	ATOM	2906	..D	LVS	435	58.244	49.748	4.137	1.00	40.31	CI
ATOM	2856	C	GLY	429	50.405	48.649	-0.716	1.00	27.39	CI	ATOM	2907	CE	LVS	435	58.293	50.861	5.213	1.00	45.32	CI
ATOM	2857	O	GLY	429	51.528	48.135	-0.741	1.00	28.51	CI	ATOM	2908	N	LVS	435	58.494	50.323	6.575	1.00	47.31	CI
ATOM	2858	N	ALA	430	50.127	49.840	-1.271	1.00	28.26	CI	ATOM	2909	II21	LVS	435	59.388	49.795	6.611	1.00	0.00	CI
ATOM	2859	II	ALA	430	49.216	50.185	-1.172	1.00	0.00	CI	ATOM	2910	II22	LVS	435	57.708	49.695	6.818	1.00	0.00	CI
ATOM	2860	CA	ALA	430	51.094	50.643	-2.015	1.00	26.04	CI	ATOM	2911	II23	LVS	435	50.534	51.109	7.237	1.00	0.00	CI
ATOM	2861	CB	ALA	430	50.490	51.976	-2.407	1.00	27.93	CI	ATOM	2912	C	LVS	435	59.906	48.135	-0.065	1.00	36.10	CI
ATOM	2862	C	ALA	430	52.300	50.927	-1.133	1.00	25.19	CI	ATOM	2913	O	LVS	435	61.139	48.036	-0.012	1.00	37.08	CI
ATOM	2863	O	ALA	430	53.393	51.053	-1.655	1.00	25.43	CI	ATOM	2914	N	LEU	436	59.215	47.168	-0.665	1.00	36.28	CI
ATOM	2864	N	ALA	431	52.171	50.979	-0.186	1.00	24.05	CI	ATOM	2915	II	LEU	436	59.235	47.245	-0.451	1.00	0.00	CI
ATOM	2865	H	ALA	431	51.279	50.872	0.579	1.00	0.00	CI	ATOM	2916	CA	LEU	436	59.793	45.994	-1.304	1.00	34.25	CI
ATOM	2866	CA	ALA	431	53.295	51.213	1.035	1.00	26.29	CI	ATOM	2917	CB	LEU	436	58.655	45.076	-1.753	1.00	33.41	CI
ATOM	2867	CB	ALA	431	52.874	51.522	2.458	1.00	24.14	CI	ATOM	2918	CG	LEU	436	57.920	44.327	-0.610	1.00	34.72	CI
ATOM	2868	C	ALA	431	54.139	49.972	1.073	1.00	29.82	CI	ATOM	2919	CD1	LEU	436	56.764	43.538	-1.181	1.00	33.50	CI
ATOM	2869	O	ALA	431	55.360	50.085	0.959	1.00	31.87	CI	ATOM	2920	CD2	LEU	436	58.080	43.375	0.117	1.00	36.39	CI
ATOM	2870	N	LEU	432	53.562	48.777	1.203	1.00	31.87	CI	ATOM	2921	C	LEU	436	60.649	46.383	-2.467	1.00	33.31	CI
ATOM	2871	H	LEU	432	52.585	48.726	1.279	1.00	0.00	CI	ATOM	2922	O	LEU	436	61.756	45.825	-2.647	1.00	33.94	CI
ATOM	2872	CA	LEU	432	54.337	47.540	1.165	1.00	33.92	CI	ATOM	2923	N	CYS	437	60.210	47.374	-3.222	1.00	32.34	CI
ATOM	2873	CB	LEU	432	53.430	46.315	1.301	1.00	37.42	CI	ATOM	2924	II	CYS	437	59.290	47.661	-3.097	1.00	0.00	CI
ATOM	2874	CG	LEU	432	54.063	44.949	1.574	1.00	37.40	CI	ATOM	2925	CA	CYS	437	60.978	47.949	-4.301	1.00	32.01	CI
ATOM	2875	CD1	LEU	432	54.751	44.949	2.950	1.00	38.10	CI	ATOM	2926	C	CYS	437	62.214	48.704	-3.857	1.00	34.70	CI
ATOM	2876	CD2	LEU	432	52.966	43.901	1.492	1.00	36.27	CI	ATOM	2927	O	CYS	437	63.094	48.840	-5.008	1.00	50.37	CI
ATOM	2877	C	LEU	432	55.996	47.404	-0.146	1.00	33.74	CI	ATOM	2928	CB	CYS	437	61.003	49.666	-6.319	1.00	36.22	CI
ATOM	2878	O	LEU	432	56.306	47.179	-0.138	1.00	33.29	CI	ATOM	2929	SG	CYS	437	62.016	49.463	-2.785	1.00	36.35	CI
ATOM	2879	N	GLN	433	54.402	47.564	-1.276	1.00	34.37	CI	ATOM	2930	N	ALA	438	61.108	49.547	-2.431	1.00	0.00	CI
ATOM	2880	II	GLN	433	53.439	47.733	-1.186	1.00	0.00	CI	ATOM	2931	II	ALA	438	63.060	50.226	-2.170	1.00	35.83	CI
ATOM	2881	CA	GLN	433	55.002	47.526	-2.600	1.00	35.83	CI	ATOM	2932	CA	ALA	438	62.440	51.107	-1.153	1.00	36.38	CI
ATOM	2882	CB	GLN	433	53.999	47.892	-3.664	1.00	35.52	CI	ATOM	2933	CB	ALA	438	64.065	49.294	-1.527	1.00	37.01	CI
ATOM	2883	CG	GLN	433	52.996	46.823	-3.832	1.00	39.40	CI	ATOM	2934	C	ALA	438	65.132	49.168	-2.092	1.00	39.39	CI
ATOM	2884	CD	GLN	433	52.049	47.097	-4.973	1.00	42.46	CI	ATOM	2935	O	ALA	438	65.338	48.591	-0.422	1.00	36.59	CI
ATOM	2885	OE1	GLN	433	50.924	47.326	-4.786	1.00	48.42	CI	ATOM	2936	N	THR	439	63.808	48.723	-0.014	1.00	0.00	CI
ATOM	2886	OE2	GLN	433	52.376	46.878	-6.725	1.00	44.77	CI	ATOM	2937	II	THR	439	62.947	48.731	0.014	1.00	0.00	CI
ATOM	2887	HE1	GLN	433	53.271	46.540	-6.433	1.00	0.00	CI	ATOM	2938	CA	THR	439	64.742	47.669	0.223	1.00	35.70	CI
ATOM	2888	HE2	GLN	433	51.693	47.087	-6.892	1.00	0.00	CI	ATOM	2939	CG	THR	439	64.073	47.042	1.040	1.00	33.34	CI
ATOM	2889	C	GLN	433	56.177	48.485	-2.757	1.00	36.48	CI	ATOM	2940	CG	THR	439	63.333	48.048	2.040	1.00	38.31	CI
ATOM	2890	O	GLN	433	57.214	48.118	-3.312	1.00	38.08	CI	ATOM	2941	IG1	THR	439	62.419	47.999	1.706	1.00	0.00	CI
ATOM	2891	N	GLU	434	56.025	49.978	-2.817	1.00	36.11	CI	ATOM	2942	CG2	THR	439	65.039	46.479	2.369	1.00	36.50	CI
ATOM	2892	H	GLU	434	55.210	49.718	-1.834	1.00	0.00	CI	ATOM	2943	C	THR	439	65.331	46.517	-0.590	1.00	36.10	CI
ATOM	2893	CA	GLU	434	57.089	50.719	-2.426	1.00	33.93	CI	ATOM	2944	O	THR	439	66.448	46.093	-0.312	1.00	36.51	CI
ATOM	2894	CB	GLU	434	56.408	51.303	-2.068	1.00	41.28	CI	ATOM	2945	N	THR	440	64.603	45.917	-1.548	1.00	36.02	CI
ATOM	2895	CG	GLU	434	57.126	53.356	-2.619	1.00	43.07	CI	ATOM	2946	II	THR	440	63.751	46.319	-1.822	1.00	34.28	CI
ATOM	2896	CD	GLU	434	57.832	53.516	-0.698	1.00	45.70	CI	ATOM	2947	CA	TYR	440	65.057	44.691	-2.198	1.00	34.78	CI
ATOM	2897	OE1	GLU	434	57.190	53.538	0.367	1.00	49.33	CI	ATOM	2948	CB	TYR	440	64.175	43.340	-0.178	1.00	33.49	CI
ATOM	2898	OE2	GLU	434	59.051	53.579	-0.760	1.00	45.45	CI	ATOM	2949	CG	TYR	440	64.016	43.420	-0.397	1.00	34.14	CI
ATOM	2899	O	GLU	434	58.257	50.348	-1.548	1.00	34.00	CI	ATOM	2950	CD1	TYR	440	62.773	43.230	0.169	1.00	35.16	CI
ATOM	2900	C	GLU	434	59.388	50.481	-1.993	1.00	32.93	CI	ATOM	2951	CD2	TYR	440	62.625	43.037	1.532	1.00	36.66	CI
ATOM	2901	N	LYS	435	58.067	49.860	-0.330	1.00	34.34	CI	ATOM	2952	CE2	TYR	440	65.176	43.064	0.385	1.00	37.83	CI
ATOM	2902	H	LYS	435	57.166	49.837	0.014	1.00	0.00	CI	ATOM	2953	CE3	TYR	440	64.992	42.881	1.752	1.00	39.02	CI
ATOM	2903	CA	LYS	435	59.151	49.010	0.511	1.00	34.56	CI	ATOM	2954	C2	TYR	440	63.741	42.864	2.317	1.00	37.34	CI
ATOM	2904	CB	LYS	435	58.577	49.010	1.847	1.00	33.89	CI	ATOM	2955	C2	TYR	440	63.637	42.649	3.678	1.00	37.56	CI
ATOM	2905	CG	LYS	435	58.357	50.231	2.709	1.00	36.71	CI	ATOM	2956	III	TYR	440	64.498	42.343	3.988	1.00	40.00	CI

FIGURE 5

ATOM	3161	CD2 LEU	472	22.501	-4.883	-2.486	1.00	56.85	C2	ATOM	3212	HE2 GLN	478	29.569	36.972	-5.317	1.00	0.00	C2
ATOM	3162	C LEU	472	23.504	40.625	-1.996	1.00	63.91	C2	ATOM	3213	HE22 GLN	478	29.641	36.928	-7.054	1.00	0.00	C2
ATOM	3163	O LEU	472	23.738	39.874	-2.949	1.00	64.90	C2	ATOM	3214	C GLN	478	33.398	38.670	-2.249	1.00	50.66	C2
ATOM	3164	HT1 LEU	472	21.563	41.441	-3.595	1.00	0.00	C2	ATOM	3215	O GLN	478	34.584	38.314	-2.217	1.00	50.13	C2
ATOM	3165	HT2 LEU	472	23.091	41.291	-4.237	1.00	0.00	C2	ATOM	3216	N LEU	479	33.045	39.909	-1.859	1.00	48.78	C2
ATOM	3166	N LEU	472	22.472	41.930	-3.693	1.00	64.29	C2	ATOM	3217	H LEU	479	32.131	40.223	-2.039	1.00	0.00	C2
ATOM	3167	HT3 LEU	472	22.358	42.849	-4.160	1.00	0.00	C2	ATOM	3218	CA LEU	479	34.015	40.800	-1.235	1.00	45.87	C2
ATOM	3168	CA LEU	472	23.092	42.037	-3.286	1.00	63.85	C2	ATOM	3219	CB LEU	479	33.434	42.141	-0.827	1.00	47.13	C2
ATOM	3169	N ALA	473	23.652	40.229	-0.733	1.00	63.02	C2	ATOM	3220	CG LEU	479	32.853	43.083	-1.818	1.00	40.40	C2
ATOM	3170	H ALA	473	23.533	40.867	0.002	1.00	0.00	C2	ATOM	3221	CD1 LEU	479	32.596	44.393	-1.078	1.00	48.15	C2
ATOM	3171	CA ALA	473	24.023	38.881	-0.353	1.00	62.37	C2	ATOM	3222	CD2 LEU	479	33.779	43.258	-3.000	1.00	48.59	C2
ATOM	3172	CB ALA	473	22.870	37.939	-0.558	1.00	63.65	C2	ATOM	3223	C LEU	479	34.505	40.146	0.056	1.00	42.15	C2
ATOM	3173	C ALA	473	25.196	38.354	-1.126	1.00	62.01	C2	ATOM	3224	O LEU	479	33.695	39.955	0.262	1.00	40.50	C2
ATOM	3174	O ALA	473	26.301	38.651	-0.715	1.00	63.36	C2	ATOM	3225	N HIS	480	33.609	39.766	0.950	1.00	49.56	C2
ATOM	3175	N GLY	474	25.032	37.784	-2.306	1.00	61.43	C2	ATOM	3226	H HIS	480	32.658	39.935	0.763	1.00	0.00	C2
ATOM	3176	H GLY	474	24.148	37.181	-2.722	1.00	0.00	C2	ATOM	3227	CA HIS	480	33.979	39.108	2.179	1.00	37.81	C2
ATOM	3177	CA GLY	474	26.101	37.137	-3.047	1.00	63.80	C2	ATOM	3228	CB HIS	480	32.742	38.214	2.922	1.00	34.29	C2
ATOM	3178	C GLY	474	27.354	37.950	-3.356	1.00	63.13	C2	ATOM	3229	CG HIS	480	33.094	38.241	4.409	1.00	33.82	C2
ATOM	3179	O GLY	474	28.482	37.417	-3.257	1.00	66.24	C2	ATOM	3230	CD2 HIS	480	33.173	36.932	4.709	1.00	33.44	C2
ATOM	3180	N CYS	475	27.175	38.237	-3.757	1.00	64.88	C2	ATOM	3231	ND1 HIS	480	33.450	38.995	5.344	1.00	34.27	C2
ATOM	3181	H CYS	475	26.261	38.550	-3.885	1.00	0.00	C2	ATOM	3232	HE1 HIS	480	33.505	39.976	5.362	1.00	0.00	C2
ATOM	3182	CA CYS	475	28.308	40.127	-4.068	1.00	61.84	C2	ATOM	3233	CD1 HIS	480	33.706	38.223	6.365	1.00	33.40	C2
ATOM	3183	C CYS	475	27.925	41.413	-4.806	1.00	63.74	C2	ATOM	3234	HE2 HIS	480	33.504	36.986	5.965	1.00	37.12	C2
ATOM	3184	SC CYS	475	29.494	42.075	-5.437	1.00	68.86	C2	ATOM	3235	HE3 HIS	480	33.637	36.202	6.544	1.00	0.00	C2
ATOM	3185	C CYS	475	28.995	40.567	-2.795	1.00	37.30	C2	ATOM	3236	C HIS	480	34.836	37.860	-1.961	1.00	49.08	C2
ATOM	3186	O CYS	475	30.214	40.449	-2.724	1.00	37.19	C2	ATOM	3237	O HIS	480	35.716	37.433	2.791	1.00	40.93	C2
ATOM	3187	N LEU	476	28.230	40.983	-1.779	1.00	33.29	C2	ATOM	3238	N SER	481	34.615	37.029	0.935	1.00	39.24	C2
ATOM	3188	H LEU	476	27.264	41.024	-1.885	1.00	0.00	C2	ATOM	3239	H SER	481	33.900	37.241	0.305	1.00	0.00	C2
ATOM	3189	CA LEU	476	28.797	41.315	-0.493	1.00	50.43	C2	ATOM	3240	CA SER	481	35.391	35.818	0.683	1.00	38.17	C2
ATOM	3190	C LEU	476	27.719	41.723	-0.323	1.00	45.68	C2	ATOM	3241	CG SER	481	34.813	34.943	-0.420	1.00	40.42	C2
ATOM	3191	CG LEU	476	27.130	43.165	-0.997	1.00	42.85	C2	ATOM	3242	OG SER	481	33.454	34.597	-0.137	1.00	42.61	C2
ATOM	3192	CD1 LEU	476	26.670	43.559	-1.896	1.00	36.20	C2	ATOM	3243	HG SER	481	32.898	35.385	-0.162	1.00	0.00	C2
ATOM	3193	CD2 LEU	476	28.160	44.180	-0.057	1.00	40.22	C2	ATOM	3244	C SER	481	36.724	36.372	0.211	1.00	36.17	C2
ATOM	3194	C LEU	476	29.546	40.108	0.042	1.00	50.42	C2	ATOM	3245	O SER	481	37.692	35.773	0.765	1.00	36.23	C2
ATOM	3195	O LEU	476	30.614	40.322	-0.646	1.00	50.61	C2	ATOM	3246	N GLY	482	36.786	37.006	-0.744	1.00	36.21	C2
ATOM	3196	N SER	477	29.053	38.922	-0.270	1.00	50.62	C2	ATOM	3247	H GLY	482	35.956	37.498	-1.168	1.00	0.00	C2
ATOM	3197	H SER	477	28.196	38.860	-0.729	1.00	0.00	C2	ATOM	3248	CA GLY	482	38.028	37.792	-1.266	1.00	36.50	C2
ATOM	3198	CA SER	477	29.721	37.712	-0.125	1.00	51.41	C2	ATOM	3249	C GLY	482	36.958	38.296	-0.151	1.00	36.14	C2
ATOM	3199	CB SER	477	28.778	36.324	-0.051	1.00	53.45	C2	ATOM	3250	O GLY	482	40.142	37.934	-0.055	1.00	36.65	C2
ATOM	3200	CG SER	477	27.732	36.616	0.926	1.00	57.65	C2	ATOM	3251	N LEU	483	38.381	39.004	0.750	1.00	44.04	C2
ATOM	3201	HG SER	477	27.280	37.462	0.828	1.00	0.00	C2	ATOM	3252	H LEU	483	37.445	39.326	0.608	1.00	0.00	C2
ATOM	3202	C SER	477	30.978	37.525	-0.681	1.00	50.75	C2	ATOM	3253	CA LEU	483	39.073	39.593	1.900	1.00	32.07	C2
ATOM	3203	O SER	477	31.980	37.143	-0.068	1.00	51.41	C2	ATOM	3254	CB LEU	483	38.134	40.442	4.721	1.00	31.17	C2
ATOM	3204	N GLN	478	31.037	37.788	-1.984	1.00	50.21	C2	ATOM	3255	CG LEU	483	37.535	41.687	2.081	1.00	30.82	C2
ATOM	3205	H GLN	478	32.022	38.056	-2.457	1.00	0.00	C2	ATOM	3256	CD1 LEU	483	36.757	42.411	3.156	1.00	40.18	C2
ATOM	3206	CA GLN	478	32.307	37.697	-2.715	1.00	51.37	C2	ATOM	3257	CD2 LEU	483	38.599	42.593	-1.480	1.00	29.50	C2
ATOM	3207	CB GLN	478	32.064	37.919	-1.166	1.00	53.65	C2	ATOM	3258	C LEU	483	39.600	38.461	2.745	1.00	32.91	C2
ATOM	3208	CG GLN	478	31.983	36.570	-4.788	1.00	57.32	C2	ATOM	3259	O LEU	483	40.752	38.498	3.199	1.00	31.45	C2
ATOM	3209	CG GLN	478	31.354	36.649	-6.160	1.00	60.47	C2	ATOM	3260	N PHE	484	38.767	37.402	2.925	1.00	44.06	C2
ATOM	3210	NE2 GLN	478	31.999	36.504	-7.205	1.00	62.76	C2	ATOM	3261	H PHE	484	37.500	37.428	2.271	1.00	0.00	C2
ATOM	3211	NE1 GLN	478	30.045	36.878	-6.167	1.00	62.16	C2	ATOM	3262	CA PHE	484	39.105	36.298	3.788	1.00	14.00	C2

FIGURE 5

ATOM 3263	CB	PIE	484	37.975	35.500	3.925	1.00	37.46	47.911	34.990	2.099	1.00	25.63	C2
ATOM 3264	CG	PIE	484	38.268	34.183	4.897	1.00	40.86	47.708	35.570	0.725	1.00	27.66	C2
ATOM 3265	CD1	PIE	484	38.219	32.884	4.482	1.00	43.62	46.761	34.755	-0.189	1.00	30.83	C2
ATOM 3266	CD2	PIE	484	38.528	34.445	6.210	1.00	43.62	46.373	35.506	-1.471	1.00	30.43	C2
ATOM 3267	CE1	PIE	484	38.421	31.858	5.395	1.00	47.98	47.472	33.454	-0.502	1.00	32.62	C2
ATOM 3268	CE2	PIE	484	38.731	33.427	7.119	1.00	46.78	48.783	35.936	2.853	1.00	25.28	C2
ATOM 3269	C	PIE	484	38.677	32.119	6.720	1.00	48.06	49.973	35.705	2.914	1.00	27.37	C2
ATOM 3270	C	PIE	484	40.245	35.602	3.113	1.00	33.92	48.237	36.935	3.534	1.00	25.79	C2
ATOM 3271	O	PIE	484	41.162	35.289	3.826	1.00	30.32	47.267	37.079	3.515	1.00	0.00	C2
ATOM 3272	H	LEU	485	40.326	35.413	1.799	1.00	32.75	49.072	37.868	4.220	1.00	25.96	C2
ATOM 3273	H	LEU	485	39.577	35.717	1.250	1.00	0.00	48.274	39.139	4.567	1.00	27.96	C2
ATOM 3274	CA	LEU	485	41.475	34.778	1.163	1.00	33.74	47.823	40.131	3.474	1.00	27.89	C2
ATOM 3275	CB	LEU	485	41.181	33.404	-2.345	1.00	41.44	46.772	41.019	4.123	1.00	28.03	C2
ATOM 3276	CD1	LEU	485	41.181	33.404	-2.345	1.00	41.44	48.988	40.942	2.899	1.00	28.15	C2
ATOM 3277	CD2	LEU	485	42.101	33.962	1.275	1.00	37.40	49.619	37.243	5.459	1.00	27.33	C2
ATOM 3278	C	LEU	485	42.740	35.503	1.376	1.00	33.95	50.740	37.528	5.865	1.00	26.73	C2
ATOM 3279	C	LEU	485	43.125	34.903	-1.899	1.00	40.07	48.883	36.370	6.111	1.00	29.88	C2
ATOM 3280	O	LEU	485	43.766	35.060	1.850	1.00	33.67	49.584	36.127	5.799	1.00	0.00	C2
ATOM 3281	N	TYR	486	42.469	36.885	1.034	1.00	33.67	49.430	35.809	7.314	1.00	33.01	C2
ATOM 3282	H	TYR	486	41.757	37.186	0.659	1.00	0.00	48.305	35.113	8.027	1.00	38.68	C2
ATOM 3283	CA	TYR	486	43.662	37.862	1.242	1.00	31.33	47.856	35.963	9.197	1.00	46.07	C2
ATOM 3284	CB	TYR	486	43.210	39.290	0.714	1.00	35.33	46.348	36.262	9.278	1.00	50.83	C2
ATOM 3285	CG	TYR	486	43.300	39.325	-0.825	1.00	33.37	45.965	37.436	9.402	1.00	51.92	C2
ATOM 3286	CD1	TYR	486	42.154	39.405	-1.579	1.00	32.70	45.425	35.294	9.278	1.00	51.67	C2
ATOM 3287	CE1	TYR	486	42.128	39.790	-2.944	1.00	31.73	45.723	34.353	9.288	1.00	0.00	C2
ATOM 3288	CE2	TYR	486	44.533	39.153	-1.445	1.00	34.53	44.489	35.560	9.286	1.00	0.00	C2
ATOM 3289	CH	TYR	486	44.618	39.033	-2.818	1.00	34.63	50.582	34.867	6.986	1.00	33.58	C2
ATOM 3290	C2	TYR	486	43.451	39.096	-3.562	1.00	35.58	51.582	34.828	7.715	1.00	34.65	C2
ATOM 3291	OH	TYR	486	43.484	38.880	-4.942	1.00	38.24	50.482	34.191	5.824	1.00	34.15	C2
ATOM 3292	H	TYR	486	42.614	39.086	-5.306	1.00	0.00	49.701	34.382	5.264	1.00	0.00	C2
ATOM 3293	C	TYR	486	44.068	37.903	2.697	1.00	27.39	51.416	33.177	5.321	1.00	31.64	C2
ATOM 3294	O	TYR	486	45.258	38.007	2.942	1.00	26.06	50.818	32.500	4.081	1.00	31.67	C2
ATOM 3295	N	GLN	487	43.270	37.491	3.708	1.00	26.95	52.802	32.678	4.959	1.00	34.79	C2
ATOM 3296	H	GLN	487	42.315	37.545	3.565	1.00	0.00	52.885	34.581	4.728	1.00	35.94	C2
ATOM 3297	CA	GLN	487	43.835	37.646	5.031	1.00	28.33	52.060	35.510	4.721	1.00	0.00	C2
ATOM 3298	CB	GLN	487	42.690	37.578	6.050	1.00	32.66	54.139	35.634	4.426	1.00	34.86	C2
ATOM 3299	CG	GLN	487	43.092	37.979	7.469	1.00	40.54	53.498	36.990	3.747	1.00	31.36	C2
ATOM 3300	CD	GLN	487	43.966	39.252	7.469	1.00	40.54	53.127	37.065	2.443	1.00	28.27	C2
ATOM 3301	OE1	GLN	487	43.441	40.346	7.292	1.00	40.45	52.715	38.495	2.214	1.00	31.74	C2
ATOM 3302	NE2	GLN	487	45.305	39.206	7.549	1.00	38.19	53.977	36.608	1.285	1.00	28.79	C2
ATOM 3303	HE2	GLN	487	45.755	40.057	7.452	1.00	0.00	54.879	35.843	5.721	1.00	36.15	C2
ATOM 3304	HE2	GLN	487	45.736	38.340	7.702	1.00	0.00	55.985	36.374	5.694	1.00	36.70	C2
ATOM 3305	C	GLN	487	44.791	36.455	5.207	1.00	28.53	54.300	35.497	6.855	1.00	38.35	C2
ATOM 3306	O	GLN	487	45.774	36.542	5.964	1.00	28.72	53.395	35.130	6.836	1.00	0.00	C2
ATOM 3307	N	GLY	488	44.550	35.363	4.454	1.00	28.32	54.910	35.648	8.157	1.00	43.14	C2
ATOM 3308	H	GLY	488	43.799	35.400	3.824	1.00	0.00	55.671	34.340	8.545	1.00	46.61	C2
ATOM 3309	CA	GLY	488	45.291	34.120	4.557	1.00	26.04	54.711	33.471	9.419	1.00	53.71	C2
ATOM 3310	C	GLY	488	46.660	34.264	4.033	1.00	25.75	54.195	32.160	8.785	1.00	60.27	C2
ATOM 3311	O	GLY	488	47.660	33.946	4.712	1.00	25.86	53.146	31.653	9.230	1.00	63.52	C2
ATOM 3312	N	LEU	489	46.655	34.798	2.818	1.00	25.05	54.839	31.630	7.862	1.00	62.76	C2
ATOM 3313	H	LEU	489	45.798	35.062	2.416	1.00	0.00						

FIGURE 5

ATOM	3365	C	GLU	494	55.865	36.825	8.343	1.00	44.32	C2
ATOM	3366	O	GLU	494	57.055	36.678	8.610	1.00	46.31	C2
ATOM	3367	N	GLY	495	55.358	38.046	8.114	1.00	44.32	C2
ATOM	3368	H	GLY	495	54.450	38.112	7.753	1.00	0.00	C2
ATOM	3369	CA	GLY	495	56.104	39.272	8.368	1.00	42.36	C2
ATOM	3370	C	GLY	495	57.015	39.695	7.238	1.00	42.33	C2
ATOM	3371	O	GLY	495	57.397	40.866	7.220	1.00	41.42	C2
ATOM	3372	N	ILE	496	57.310	38.802	6.279	1.00	41.04	C2
ATOM	3373	H	ILE	496	56.927	37.906	6.374	1.00	0.00	C2
ATOM	3374	CA	ILE	496	58.259	38.993	5.192	1.00	41.15	C2
ATOM	3375	CB	ILE	496	57.929	40.216	4.253	1.00	38.60	C2
ATOM	3376	CG2	ILE	496	59.077	40.437	3.248	1.00	37.62	C2
ATOM	3377	CG1	ILE	496	56.662	39.964	3.480	1.00	36.59	C2
ATOM	3378	CD	ILE	496	56.314	41.071	2.470	1.00	35.27	C2
ATOM	3379	C	ILE	496	59.672	39.203	5.749	1.00	42.91	C2
ATOM	3380	O	ILE	496	60.541	38.396	5.448	1.00	44.22	C2
ATOM	3381	N	SER	497	59.998	40.228	6.333	1.00	44.31	C2
ATOM	3382	H	SER	497	59.297	40.852	6.827	1.00	0.00	C2
ATOM	3383	CA	SER	497	61.346	40.501	6.992	1.00	44.86	C2
ATOM	3384	CB	SER	497	62.204	41.254	5.938	1.00	44.13	C2
ATOM	3385	CG	SER	497	62.181	42.673	6.033	1.00	40.74	C2
ATOM	3386	HC	SER	497	62.531	42.964	5.170	1.00	0.00	C2
ATOM	3387	C	SER	497	61.164	41.413	8.185	1.00	45.85	C2
ATOM	3388	O	SER	497	60.132	42.110	8.288	1.00	47.55	C2
ATOM	3389	N	PRO	498	62.164	41.490	9.071	1.00	44.96	C2
ATOM	3390	CD	PRO	498	63.318	40.621	9.126	1.00	42.33	C2
ATOM	3391	CA	PRO	498	62.086	42.327	10.250	1.00	44.88	C2
ATOM	3392	CB	PRO	498	63.431	42.038	10.885	1.00	45.13	C2
ATOM	3393	CG	PRO	498	63.629	40.581	10.603	1.00	42.00	C2
ATOM	3394	C	PRO	498	61.760	43.799	9.983	1.00	45.22	C2
ATOM	3395	O	PRO	498	61.215	44.446	10.869	1.00	45.24	C2
ATOM	3396	N	GLU	499	62.017	44.314	8.777	1.00	46.16	C2
ATOM	3397	H	GLU	499	62.362	43.716	8.081	1.00	0.00	C2
ATOM	3398	CA	GLU	499	61.731	45.699	8.391	1.00	48.06	C2
ATOM	3399	CB	GLU	499	62.498	46.193	7.155	1.00	52.19	C2
ATOM	3400	CG	GLU	499	64.001	46.187	7.100	1.00	37.51	C2
ATOM	3401	CD	GLU	499	64.544	44.737	7.076	1.00	60.61	C2
ATOM	3402	OE1	GLU	499	64.755	44.231	8.162	1.00	62.96	C2
ATOM	3403	OE2	GLU	499	64.739	44.234	5.984	1.00	62.79	C2
ATOM	3404	C	GLU	499	60.269	45.896	7.981	1.00	46.94	C2
ATOM	3405	O	GLU	499	59.600	46.895	8.272	1.00	48.15	C2
ATOM	3406	N	LEU	500	59.806	44.934	7.193	1.00	44.38	C2
ATOM	3407	H	LEU	500	60.151	44.137	7.027	1.00	0.00	C2
ATOM	3408	CA	LEU	500	58.491	44.997	6.651	1.00	41.08	C2
ATOM	3409	CB	LEU	500	58.519	44.197	5.445	1.00	42.70	C2
ATOM	3410	CG	LEU	500	59.303	44.862	4.351	1.00	41.98	C2
ATOM	3411	CD1	LEU	500	59.776	43.828	3.251	1.00	43.04	C2
ATOM	3412	CD2	LEU	500	58.427	45.874	3.671	1.00	45.04	C2
ATOM	3413	C	LEU	500	57.455	44.521	7.628	1.00	40.59	C2
ATOM	3414	O	LEU	500	56.274	44.835	7.463	1.00	40.69	C2
ATOM	3415	N	GLY	501	57.866	43.835	8.685	1.00	39.37	C2
ATOM	3416	H	GLY	501	58.808	43.579	8.730	1.00	0.00	C2
ATOM	3417	CA	GLY	501	56.974	43.386	9.754	1.00	39.59	C2
ATOM	3418	C	GLY	501	55.816	44.324	10.092	1.00	39.66	C2
ATOM	3419	O	GLY	501	54.661	44.034	9.777	1.00	40.66	C2
ATOM	3420	N	PRO	502	55.986	45.462	10.742	1.00	39.90	C2
ATOM	3421	CD	PRO	502	57.227	45.908	11.335	1.00	41.18	C2
ATOM	3422	CB	PRO	502	54.912	46.387	11.045	1.00	38.67	C2
ATOM	3423	CG	PRO	502	55.594	47.494	11.791	1.00	39.23	C2
ATOM	3424	CG	PRO	502	56.989	47.405	11.221	1.00	41.36	C2
ATOM	3425	C	PRO	502	54.158	46.849	9.817	1.00	37.54	C2
ATOM	3426	O	PRO	502	52.966	47.139	9.961	1.00	38.36	C2
ATOM	3427	H	THR	503	54.728	46.887	8.649	1.00	35.13	C2
ATOM	3428	H	THR	503	55.663	46.638	8.449	1.00	0.00	C2
ATOM	3429	CA	THR	503	53.940	47.283	7.462	1.00	35.09	C2
ATOM	3430	CB	THR	503	54.832	47.376	6.245	1.00	34.48	C2
ATOM	3431	CG1	THR	503	56.035	48.018	6.668	1.00	38.23	C2
ATOM	3432	CG2	THR	503	55.837	48.946	6.845	1.00	0.00	C2
ATOM	3433	C	THR	503	54.197	48.162	5.126	1.00	35.56	C2
ATOM	3434	C	THR	503	52.836	46.232	7.215	1.00	35.37	C2
ATOM	3435	O	THR	503	51.671	46.532	6.915	1.00	37.11	C2
ATOM	3436	N	LEU	504	53.218	44.996	7.380	1.00	34.02	C2
ATOM	3437	H	LEU	504	54.146	44.799	7.647	1.00	0.00	C2
ATOM	3438	CA	LEU	504	52.301	43.912	7.173	1.00	32.50	C2
ATOM	3439	CB	LEU	504	53.127	42.650	7.002	1.00	34.78	C2
ATOM	3440	CG	LEU	504	53.464	42.256	5.601	1.00	34.07	C2
ATOM	3441	CD1	LEU	504	54.163	40.977	5.667	1.00	37.97	C2
ATOM	3442	CD2	LEU	504	52.254	41.865	4.809	1.00	37.34	C2
ATOM	3443	C	LEU	504	51.324	43.821	8.328	1.00	29.54	C2
ATOM	3444	O	LEU	504	50.141	43.562	8.078	1.00	30.40	C2
ATOM	3445	N	ASP	505	51.736	44.106	9.551	1.00	26.49	C2
ATOM	3446	H	ASP	505	52.689	44.269	9.699	1.00	0.00	C2
ATOM	3447	CA	ASP	505	50.798	44.084	10.643	1.00	27.88	C2
ATOM	3448	CB	ASP	505	51.446	44.345	11.926	1.00	29.86	C2
ATOM	3449	CG	ASP	505	52.663	42.298	11.534	1.00	41.04	C2
ATOM	3450	CD1	ASP	505	53.179	43.542	13.224	1.00	37.40	C2
ATOM	3451	C	ASP	505	49.661	45.060	10.568	1.00	28.61	C2
ATOM	3452	O	ASP	505	48.566	44.739	11.039	1.00	30.30	C2
ATOM	3453	N	THR	506	49.894	46.242	10.002	1.00	28.29	C2
ATOM	3454	H	THR	506	50.823	46.493	9.804	1.00	0.00	C2
ATOM	3455	CA	THR	506	48.860	47.223	9.731	1.00	25.74	C2
ATOM	3456	CB	THR	506	49.944	49.099	10.588	1.00	31.63	C2
ATOM	3457	CG1	THR	506	49.243	49.072	11.246	1.00	0.00	C2
ATOM	3458	CG2	THR	506	48.594	49.517	8.619	1.00	24.46	C2
ATOM	3459	C	THR	506	48.022	46.735	8.615	1.00	24.00	C2
ATOM	3460	O	THR	506	46.817	46.864	8.719	1.00	25.85	C2
ATOM	3461	N	LEU	507	48.554	46.196	7.525	1.00	23.51	C2
ATOM	3462	H	LEU	507	49.527	46.073	7.453	1.00	0.00	C2
ATOM	3463	CA	LEU	507	47.682	45.770	6.434	1.00	23.85	C2
ATOM	3464	CB	LEU	507	48.574	45.408	5.196	1.00	23.13	C2

FIGURE 5

ATOM	3467	CG	LEU	507	48.010	-919	3.858	1.00	20.85	C2
ATOM	3468	CD1	LEU	507	46.771	45.650	3.455	1.00	24.13	C2
ATOM	3469	CD2	LEU	507	49.074	45.055	2.842	1.00	20.13	C2
ATOM	3470	C	LEU	507	46.766	44.640	6.880	1.00	24.09	C2
ATOM	3471	O	LEU	507	45.600	44.764	6.541	1.00	25.60	C2
ATOM	3472	N	GLN	508	47.152	43.618	7.661	1.00	24.01	C2
ATOM	3473	H	GLN	508	48.112	43.555	7.866	1.00	0.00	C2
ATOM	3474	CA	GLN	508	46.228	42.625	8.214	1.00	23.71	C2
ATOM	3475	CB	GLN	508	46.961	41.627	9.036	1.00	23.83	C2
ATOM	3476	CD	GLN	508	47.937	40.899	8.173	1.00	31.64	C2
ATOM	3477	CE	GLN	508	48.842	40.080	9.054	1.00	34.00	C2
ATOM	3478	OE1	GLN	508	50.031	40.346	9.161	1.00	36.30	C2
ATOM	3479	NE2	GLN	508	48.321	39.090	9.748	1.00	36.30	C2
ATOM	3480	HE1	GLN	508	47.373	38.880	9.639	1.00	0.00	C2
ATOM	3481	HE2	GLN	508	48.891	38.636	10.406	1.00	0.00	C2
ATOM	3482	C	GLN	508	45.105	43.123	9.111	1.00	24.24	C2
ATOM	3483	O	GLN	508	43.978	42.650	9.014	1.00	24.06	C2
ATOM	3484	N	LEU	509	45.375	44.019	10.090	1.00	26.07	C2
ATOM	3485	H	LEU	509	46.316	44.262	10.222	1.00	0.00	C2
ATOM	3486	CA	LEU	509	44.378	44.640	10.977	1.00	25.71	C2
ATOM	3487	CB	LEU	509	44.983	45.555	12.031	1.00	25.60	C2
ATOM	3488	CG	LEU	509	45.838	44.757	13.042	1.00	25.60	C2
ATOM	3489	CD1	LEU	509	46.658	45.705	13.886	1.00	28.93	C2
ATOM	3490	CD2	LEU	509	44.950	43.919	13.937	1.00	27.94	C2
ATOM	3491	C	LEU	509	43.465	45.471	10.130	1.00	25.17	C2
ATOM	3492	O	LEU	509	42.274	45.411	10.408	1.00	27.22	C2
ATOM	3493	N	ASP	510	43.899	46.208	9.101	1.00	23.77	C2
ATOM	3494	H	ASP	510	44.865	46.277	8.930	1.00	0.00	C2
ATOM	3495	CA	ASP	510	42.955	46.898	8.240	1.00	22.66	C2
ATOM	3496	CB	ASP	510	43.652	47.829	7.306	1.00	25.21	C2
ATOM	3497	CG	ASP	510	44.316	48.966	8.068	1.00	33.01	C2
ATOM	3498	OD1	ASP	510	45.178	49.621	7.477	1.00	34.28	C2
ATOM	3499	OD2	ASP	510	43.988	49.209	9.250	1.00	34.44	C2
ATOM	3500	C	ASP	510	42.104	45.980	7.398	1.00	23.72	C2
ATOM	3501	O	ASP	510	40.897	46.220	7.387	1.00	24.80	C2
ATOM	3502	N	VAL	511	42.632	44.984	6.659	1.00	22.38	C2
ATOM	3503	H	VAL	511	43.611	44.980	6.620	1.00	0.00	C2
ATOM	3504	CA	VAL	511	41.823	44.010	5.961	1.00	21.89	C2
ATOM	3505	CB	VAL	511	42.752	42.924	5.366	1.00	22.71	C2
ATOM	3506	CG	VAL	511	41.954	41.756	4.792	1.00	20.43	C2
ATOM	3507	CG2	VAL	511	43.539	43.524	4.210	1.00	16.19	C2
ATOM	3508	C	VAL	511	40.827	43.403	6.960	1.00	21.92	C2
ATOM	3509	O	VAL	511	39.625	43.447	6.719	1.00	23.46	C2
ATOM	3510	N	ALA	512	41.258	43.017	8.163	1.00	20.49	C2
ATOM	3511	H	ALA	512	42.216	43.063	8.361	1.00	0.00	C2
ATOM	3512	CA	ALA	512	40.388	42.357	9.108	1.00	20.83	C2
ATOM	3513	CB	ALA	512	41.103	41.974	10.344	1.00	17.89	C2
ATOM	3514	C	ALA	512	39.250	42.705	9.550	1.00	23.89	C2
ATOM	3515	O	ALA	512	38.201	42.668	9.874	1.00	24.61	C2
ATOM	3516	N	ASP	513	39.417	44.539	9.544	1.00	25.96	C2
ATOM	3517	H	ASP	513	40.300	44.888	9.291	1.00	0.00	C2
ATOM	3518	CA	ASP	513	38.374	45.471	9.947	1.00	25.37	C2
ATOM	3519	CG	ASP	513	38.958	46.787	10.373	1.00	26.88	C2
ATOM	3520	CG	ASP	513	39.682	46.679	11.712	1.00	32.35	C2
ATOM	3521	OD1	ASP	513	40.371	47.644	12.058	1.00	35.06	C2
ATOM	3522	OD2	ASP	513	39.580	45.646	12.390	1.00	34.10	C2
ATOM	3523	C	ASP	513	37.392	45.730	8.846	1.00	24.95	C2
ATOM	3524	O	ASP	513	36.185	45.868	9.090	1.00	26.92	C2
ATOM	3525	N	PIE	514	37.867	45.739	7.634	1.00	22.88	C2
ATOM	3526	H	PIE	514	38.829	45.614	7.475	1.00	0.00	C2
ATOM	3527	CA	PIE	514	36.974	45.922	6.530	1.00	24.09	C2
ATOM	3528	CB	PIE	514	37.812	46.061	5.266	1.00	18.11	C2
ATOM	3529	CG	PIE	514	36.956	46.470	4.072	1.00	12.46	C2
ATOM	3530	CD1	PIE	514	35.715	47.089	4.245	1.00	15.18	C2
ATOM	3531	CD2	PIE	514	37.440	46.197	2.804	1.00	13.77	C2
ATOM	3532	CE1	PIE	514	34.983	47.419	3.130	1.00	14.53	C2
ATOM	3533	CE2	PIE	514	36.693	46.539	1.705	1.00	12.10	C2
ATOM	3534	C	PIE	514	35.468	47.146	1.868	1.00	10.68	C2
ATOM	3535	C	PIE	514	36.076	44.703	6.450	1.00	29.23	C2
ATOM	3536	O	PIE	514	34.788	44.828	6.350	1.00	29.80	C2
ATOM	3537	N	ALA	515	36.694	43.490	6.331	1.00	31.15	C2
ATOM	3538	H	ALA	515	37.581	43.450	6.639	1.00	1.00	C2
ATOM	3539	CA	ALA	515	35.839	42.260	6.416	1.00	32.36	C2
ATOM	3540	CB	ALA	515	36.851	41.126	6.402	1.00	32.35	C2
ATOM	3541	C	ALA	515	34.801	42.089	7.535	1.00	32.39	C2
ATOM	3542	O	ALA	515	33.676	41.609	7.331	1.00	32.63	C2
ATOM	3543	N	THR	516	35.164	42.457	8.735	1.00	33.01	C2
ATOM	3544	H	THR	516	36.117	42.578	8.935	1.00	0.00	C2
ATOM	3545	CA	THR	516	34.231	42.566	9.821	1.00	35.18	C2
ATOM	3546	CB	THR	516	35.016	43.018	10.988	1.00	35.40	C2
ATOM	3547	CG1	THR	516	35.685	41.818	11.336	1.00	42.65	C2
ATOM	3548	CG2	THR	516	36.505	41.713	10.816	1.00	0.00	C2
ATOM	3549	C	THR	516	34.262	43.672	12.097	1.00	35.56	C2
ATOM	3550	C	THR	516	33.140	43.554	9.482	1.00	37.62	C2
ATOM	3551	O	THR	516	32.005	43.315	9.857	1.00	40.37	C2
ATOM	3552	N	THR	517	33.387	44.666	8.802	1.00	38.61	C2
ATOM	3553	H	THR	517	34.291	44.850	8.469	1.00	0.00	C2
ATOM	3554	CA	THR	517	32.359	45.641	8.512	1.00	38.92	C2
ATOM	3555	CB	THR	517	33.123	46.903	7.962	1.00	40.46	C2
ATOM	3556	CG1	THR	517	33.832	47.429	9.103	1.00	43.22	C2
ATOM	3557	CG2	THR	517	34.536	46.815	9.335	1.00	0.00	C2
ATOM	3558	C	THR	517	32.232	47.926	7.253	1.00	39.90	C2
ATOM	3559	C	THR	517	31.343	45.012	7.551	1.00	38.30	C2
ATOM	3560	O	THR	517	30.137	45.123	7.811	1.00	38.69	C2
ATOM	3561	N	ILE	518	31.790	44.344	6.466	1.00	37.54	C2
ATOM	3562	H	ILE	518	32.756	44.386	6.297	1.00	0.00	C2
ATOM	3563	CA	ILE	518	30.923	43.646	5.510	1.00	16.10	C2
ATOM	3564	CB	ILE	518	31.699	42.912	4.439	1.00	31.81	C2
ATOM	3565	CG1	ILE	518	30.703	42.202	3.555	1.00	33.46	C2
ATOM	3566	CG2	ILE	518	32.623	43.842	3.699	1.00	32.91	C2
ATOM	3567	CD	ILE	518	32.019	44.700	2.596	1.00	44.89	C2
ATOM	3568	C	ILE	518	30.172	42.591	6.317	1.00	38.43	C2

FIGURE 5

ATOM 3569 O HLE S18	28.938	4.145	6.205	1.00	39.93	C2
ATOM 3570 N TRP S19	30.842	41.785	7.179	1.00	38.64	C2
ATOM 3571 C TRP S19	31.785	41.959	7.361	1.00	0.00	C2
ATOM 3572 CA TRP S19	30.144	40.784	7.945	1.00	38.15	C2
ATOM 3573 CB TRP S19	31.124	40.083	8.780	1.00	38.52	C2
ATOM 3574 CG TRP S19	30.493	38.793	9.255	1.00	42.26	C2
ATOM 3575 CD TRP S19	29.880	38.578	10.473	1.00	41.70	C2
ATOM 3576 CE2 TRP S19	29.437	37.278	10.335	1.00	41.69	C2
ATOM 3577 CE1 TRP S19	29.648	39.202	11.629	1.00	42.26	C2
ATOM 3578 CD1 TRP S19	30.448	37.695	8.419	1.00	42.92	C2
ATOM 3579 NE1 TRP S19	29.788	36.793	9.115	1.00	44.19	C2
ATOM 3580 NE2 TRP S19	29.485	35.935	8.741	1.00	41.91	C2
ATOM 3581 C22 TRP S19	28.753	36.671	11.360	1.00	41.91	C2
ATOM 3582 C23 TRP S19	28.964	38.666	12.652	1.00	41.77	C2
ATOM 3583 CH2 TRP S19	28.027	37.375	12.515	1.00	41.05	C2
ATOM 3584 C TRP S19	27.888	40.919	8.726	1.00	38.28	C2
ATOM 3585 O TRP S19	29.264	42.375	9.650	1.00	41.86	C2
ATOM 3586 N GUN S20	30.180	42.717	9.700	1.00	0.00	C2
ATOM 3587 H GUN S20	28.240	43.016	10.464	1.00	44.63	C2
ATOM 3588 CA GUN S20	28.691	44.198	11.239	1.00	47.05	C2
ATOM 3589 CB GUN S20	29.602	43.808	12.360	1.00	54.78	C2
ATOM 3590 CG GUN S20	29.910	45.009	13.243	1.00	60.14	C2
ATOM 3591 CD GUN S20	28.988	45.566	13.854	1.00	61.62	C2
ATOM 3592 CE1 GUN S20	31.172	45.456	13.371	1.00	60.46	C2
ATOM 3593 CE2 GUN S20	31.289	46.260	13.910	1.00	0.00	C2
ATOM 3594 HE21 GUN S20	31.895	44.966	12.932	1.00	0.00	C2
ATOM 3595 HE22 GUN S20	27.141	43.577	9.621	1.00	46.28	C2
ATOM 3596 C GUN S20	26.001	43.474	10.059	1.00	48.62	C2
ATOM 3597 O GUN S20	27.362	44.145	8.442	1.00	46.99	C2
ATOM 3598 N GUN S21	28.272	44.257	8.092	1.00	0.00	C2
ATOM 3599 H GUN S21	26.226	44.638	7.716	1.00	49.02	C2
ATOM 3600 CA GUN S21	26.632	45.553	6.566	1.00	50.06	C2
ATOM 3601 CB GUN S21	25.456	46.226	5.790	1.00	50.87	C2
ATOM 3602 CG GUN S21	24.616	47.278	6.534	1.00	51.82	C2
ATOM 3603 CD GUN S21	24.864	47.694	7.671	1.00	52.47	C2
ATOM 3604 CE1 GUN S21	23.577	47.776	5.888	1.00	50.36	C2
ATOM 3605 NE2 GUN S21	23.392	47.455	4.987	1.00	0.00	C2
ATOM 3606 HE21 GUN S21	23.044	48.424	6.390	1.00	0.00	C2
ATOM 3607 HE22 GUN S21	25.454	43.446	7.155	1.00	50.15	C2
ATOM 3608 C GUN S21	24.214	43.514	7.177	1.00	51.82	C2
ATOM 3609 O GUN S22	26.037	42.348	6.668	1.00	49.18	C2
ATOM 3610 N MET S22	27.038	42.291	6.688	1.00	0.00	C2
ATOM 3611 H MET S22	25.280	41.227	6.171	1.00	48.22	C2
ATOM 3612 CA MET S22	26.185	40.167	5.607	1.00	46.36	C2
ATOM 3613 CB MET S22	26.942	40.661	4.412	1.00	44.32	C2
ATOM 3614 CG MET S22	27.855	39.435	3.426	1.00	48.35	C2
ATOM 3615 CD MET S22	28.795	38.447	4.565	1.00	42.80	C2
ATOM 3616 CE MET S22	24.453	40.642	7.316	1.00	50.14	C2
ATOM 3617 C MET S22	23.380	40.124	7.038	1.00	50.60	C2
ATOM 3618 O MET S22	24.848	40.722	8.596	1.00	51.91	C2
ATOM 3619 N GUN S23						C2
ATOM 3620 H GUN S23	25.766	41.031	8.769	1.00	0.00	C2
ATOM 3621 CA GUN S23	24.027	40.313	9.718	1.00	54.53	C2
ATOM 3622 CB GUN S23	24.654	40.486	11.081	1.00	54.50	C2
ATOM 3623 CG GUN S23	25.732	39.525	11.398	1.00	57.05	C2
ATOM 3624 CD GUN S23	25.386	38.150	10.888	1.00	61.72	C2
ATOM 3625 CE1 GUN S23	24.515	37.487	11.477	1.00	64.60	C2
ATOM 3626 CE2 GUN S23	25.979	37.773	9.872	1.00	63.15	C2
ATOM 3627 C GUN S23	22.773	41.116	9.836	1.00	58.29	C2
ATOM 3628 O GUN S23	21.688	40.538	9.850	1.00	54.32	C2
ATOM 3629 H ALA S24	22.920	42.432	9.932	1.00	61.41	C2
ATOM 3630 N ALA S24	23.834	42.798	10.024	1.00	0.00	C2
ATOM 3631 CA ALA S24	21.815	43.360	10.076	1.00	63.58	C2
ATOM 3632 CB ALA S24	22.312	44.768	9.992	1.00	54.11	C2
ATOM 3633 CG ALA S24	20.818	43.109	8.946	1.00	64.79	C2
ATOM 3634 O ALA S24	19.555	42.824	9.206	1.00	65.69	C2
ATOM 3635 N ALA S25	21.251	43.083	7.693	1.00	66.44	C2
ATOM 3636 H ALA S25	22.196	43.283	7.516	1.00	0.00	C2
ATOM 3637 CA ALA S25	20.371	42.789	6.574	1.00	68.58	C2
ATOM 3638 CB ALA S25	21.117	43.044	5.288	1.00	67.42	C2
ATOM 3639 C ALA S25	19.841	41.356	6.558	1.00	71.13	C2
ATOM 3640 O ALA S25	19.116	40.946	5.651	1.00	71.65	C2
ATOM 3641 N GLY S26	20.257	40.510	7.498	1.00	74.20	C2
ATOM 3642 H GLY S26	21.019	40.780	8.043	1.00	0.00	C2
ATOM 3643 CA GLY S26	19.728	39.157	7.653	1.00	76.30	C2
ATOM 3644 C GLY S26	20.430	38.085	6.842	1.00	78.19	C2
ATOM 3645 O GLY S26	20.174	36.910	7.094	1.00	79.05	C2
ATOM 3646 N MET S27	21.388	38.433	5.970	1.00	80.23	C2
ATOM 3647 H MET S27	21.759	39.337	6.075	1.00	0.00	C2
ATOM 3648 CA MET S27	22.055	37.489	5.063	1.00	81.73	C2
ATOM 3649 CB MET S27	22.771	38.256	3.928	1.00	81.72	C2
ATOM 3650 CG MET S27	22.385	39.719	3.720	1.00	83.52	C2
ATOM 3651 SD MET S27	23.364	40.523	2.436	1.00	87.44	C2
ATOM 3652 CF MET S27	22.600	42.117	2.403	1.00	84.47	C2
ATOM 3653 C MET S27	23.078	36.584	5.780	1.00	82.04	C2
ATOM 3654 OT1 MET S27	22.974	35.357	5.624	1.00	83.38	C2
ATOM 3655 OT2 MET S27	23.949	37.104	6.500	1.00	82.90	C2
ATOM 3656 CB MET S28	47.224	28.531	2.401	1.00	77.43	C3
ATOM 3657 CG MET S28	47.397	30.041	2.427	1.00	77.15	C3
ATOM 3658 SD MET S28	46.205	30.708	3.604	1.00	79.03	C3
ATOM 3659 CF MET S28	44.850	31.067	2.515	1.00	77.20	C3
ATOM 3660 C MET S28	48.549	27.839	0.386	1.00	75.22	C3
ATOM 3661 O MET S28	49.130	26.745	0.405	1.00	77.11	C3
ATOM 3662 HT1 MET S28	47.563	26.068	1.449	1.00	0.00	C3
ATOM 3663 HT2 MET S28	46.638	26.204	0.075	1.00	0.00	C3
ATOM 3664 N MET S28	46.724	26.552	1.050	1.00	77.52	C3
ATOM 3665 HT3 MET S28	45.873	26.401	1.617	1.00	0.00	C3
ATOM 3666 CA MET S28	47.153	27.940	0.995	1.00	76.57	C3
ATOM 3667 N PRO S29	49.089	28.870	-0.224	1.00	72.65	C3
ATOM 3668 CD PRO S29	48.346	29.821	-1.046	1.00	72.46	C3
ATOM 3669 CA PRO S29	50.526	29.020	-0.349	1.00	70.34	C3
ATOM 3670 CB PRO S29	50.677	30.765	-1.096	1.00	71.99	C3

FIGURE 5

ATOM 3671 CG PRO 539	-49.437	30.503	-1.837	1.00	71.52	C3
ATOM 3672 C PRO 539	51.250	28.931	0.991	1.00	67.83	C3
ATOM 3673 O PRO 539	50.666	29.294	2.029	1.00	68.05	C3
ATOM 3674 N ALA 540	52.484	28.417	0.961	1.00	64.48	C3
ATOM 3675 H ALA 540	52.858	28.098	0.111	1.00	0.00	C3
ATOM 3676 CA ALA 540	53.389	28.498	2.112	1.00	61.83	C3
ATOM 3677 CB ALA 540	54.004	27.200	2.619	1.00	63.57	C3
ATOM 3678 C ALA 540	54.559	29.212	1.496	1.00	58.74	C3
ATOM 3679 O ALA 540	54.835	29.036	0.301	1.00	58.30	C3
ATOM 3680 N PHE 541	55.256	30.008	2.292	1.00	55.25	C3
ATOM 3681 H PHE 541	55.093	30.068	3.257	1.00	0.00	C3
ATOM 3682 CA PHE 541	56.299	30.814	1.702	1.00	51.38	C3
ATOM 3683 CB PHE 541	55.964	32.306	1.942	1.00	48.80	C3
ATOM 3684 CG PHE 541	54.789	32.703	1.058	1.00	45.77	C3
ATOM 3685 CD1 PHE 541	54.992	32.939	-0.279	1.00	44.20	C3
ATOM 3686 CD2 PHE 541	53.507	32.747	1.582	1.00	43.98	C3
ATOM 3687 CE1 PHE 541	53.901	33.207	-1.074	1.00	43.98	C3
ATOM 3688 CE2 PHE 541	52.428	33.018	0.769	1.00	42.86	C3
ATOM 3689 C PHE 541	52.625	33.247	-0.563	1.00	42.52	C3
ATOM 3690 O PHE 541	57.586	30.364	2.333	1.00	49.80	C3
ATOM 3691 N ALA 542	58.002	30.807	3.395	1.00	49.55	C3
ATOM 3692 H ALA 542	58.172	29.442	1.562	1.00	48.21	C3
ATOM 3693 H ALA 542	57.825	29.298	0.656	1.00	0.00	C3
ATOM 3694 CA ALA 542	59.326	28.711	1.968	1.00	45.37	C3
ATOM 3695 CB ALA 542	59.700	27.749	0.898	1.00	45.21	C3
ATOM 3696 C ALA 542	60.510	29.567	2.266	1.00	44.87	C3
ATOM 3697 O ALA 542	61.013	29.504	3.374	1.00	46.49	C3
ATOM 3698 H SER 543	61.013	30.408	1.395	1.00	0.00	C3
ATOM 3699 H SER 543	60.477	30.685	0.630	1.00	0.00	C3
ATOM 3700 CA SER 543	62.253	31.108	1.708	1.00	40.31	C3
ATOM 3701 CB SER 543	63.170	30.861	0.587	1.00	37.74	C3
ATOM 3702 CG SER 543	62.391	31.181	-0.554	1.00	35.74	C3
ATOM 3703 HG SER 543	61.824	30.423	-0.751	1.00	0.00	C3
ATOM 3704 C SER 543	62.087	32.613	1.896	1.00	40.88	C3
ATOM 3705 O SER 543	61.016	33.115	1.536	1.00	42.63	C3
ATOM 3706 N ALA 544	63.120	33.383	2.310	1.00	38.84	C3
ATOM 3707 H ALA 544	63.929	32.951	2.650	1.00	0.00	C3
ATOM 3708 CA ALA 544	63.035	34.836	2.345	1.00	37.31	C3
ATOM 3709 CB ALA 544	64.340	35.450	2.808	1.00	35.74	C3
ATOM 3710 C ALA 544	62.723	35.372	0.947	1.00	37.06	C3
ATOM 3711 O ALA 544	61.879	36.220	0.820	1.00	38.23	C3
ATOM 3712 H PHE 545	64.131	34.298	-0.010	1.00	0.00	C3
ATOM 3713 H PHE 545	62.992	35.268	-1.484	1.00	33.66	C3
ATOM 3714 CA PHE 545	63.758	34.534	-2.593	1.00	29.71	C3
ATOM 3715 CB PHE 545	63.140	34.742	-3.990	1.00	29.62	C3
ATOM 3716 CG PHE 545	62.317	35.788	-4.557	1.00	29.80	C3
ATOM 3717 CD1 PHE 545	63.371	35.915	-4.689	1.00	31.90	C3
ATOM 3718 CD2 PHE 545	61.723	33.984	-5.795	1.00	28.61	C3
ATOM 3719 CE1 PHE 545	62.777	36.113	-5.928	1.00	31.00	C3
ATOM 3720 CE2 PHE 545	61.955	35.150	-6.480	1.00	31.01	C3
ATOM 3721 CZ PHE 545						
ATOM 3722 C PHE 545	61.543	34.900	-1.667	1.00	34.81	C3
ATOM 3723 O PHE 545	60.901	35.660	-2.389	1.00	38.88	C3
ATOM 3724 N GIN 546	60.912	33.847	-1.135	1.00	34.77	C3
ATOM 3725 H GIN 546	61.396	33.223	-0.558	1.00	0.00	C3
ATOM 3726 CA GIN 546	59.490	33.637	-1.433	1.00	33.72	C3
ATOM 3727 CB GIN 546	59.145	32.232	-1.140	1.00	34.85	C3
ATOM 3728 CG GIN 546	59.582	31.585	-2.444	1.00	42.45	C3
ATOM 3729 CD GIN 546	59.374	30.085	-2.473	1.00	46.05	C3
ATOM 3730 OE1 GIN 546	59.287	29.472	-1.394	1.00	48.90	C3
ATOM 3731 NE2 GIN 546	59.339	29.442	-3.644	1.00	47.20	C3
ATOM 3732 HE2 GIN 546	59.476	29.948	-4.472	1.00	0.00	C3
ATOM 3733 HE3 GIN 546	59.154	28.481	-3.609	1.00	0.00	C3
ATOM 3734 C GIN 546	58.504	34.541	-0.729	1.00	31.62	C3
ATOM 3735 O GIN 546	57.429	34.850	-1.233	1.00	29.88	C3
ATOM 3736 N ARG 547	58.907	34.929	0.465	1.00	31.09	C3
ATOM 3737 H ARG 547	59.750	34.566	0.811	1.00	0.00	C3
ATOM 3738 CA ARG 547	58.160	35.830	1.282	1.00	31.43	C3
ATOM 3739 CB ARG 547	58.813	35.874	2.601	1.00	31.74	C3
ATOM 3740 CG ARG 547	57.906	35.224	3.623	1.00	37.02	C3
ATOM 3741 CD ARG 547	58.344	33.858	4.076	1.00	40.56	C3
ATOM 3742 NE ARG 547	59.743	34.058	4.345	1.00	47.90	C3
ATOM 3743 IE ARG 547	60.389	33.924	3.620	1.00	0.00	C3
ATOM 3744 CZ ARG 547	60.190	34.394	5.543	1.00	49.48	C3
ATOM 3745 NH1 ARG 547	59.361	34.522	6.593	1.00	51.97	C3
ATOM 3746 NH11 ARG 547	58.380	34.356	6.488	1.00	0.00	C3
ATOM 3747 NH12 ARG 547	59.731	34.763	7.491	1.00	0.00	C3
ATOM 3748 NH2 ARG 547	61.464	34.775	5.616	1.00	48.53	C3
ATOM 3749 NH21 ARG 547	62.025	34.803	4.788	1.00	0.00	C3
ATOM 3750 NH22 ARG 547	61.854	35.034	6.501	1.00	0.00	C3
ATOM 3751 C ARG 547	58.167	37.181	0.590	1.00	32.26	C3
ATOM 3752 O ARG 547	57.084	37.694	0.317	1.00	34.25	C3
ATOM 3753 N ARG 548	59.348	37.717	0.205	1.00	31.44	C3
ATOM 3754 H ARG 548	60.148	37.203	0.444	1.00	0.00	C3
ATOM 3755 CA ARG 548	59.579	38.980	-0.555	1.00	30.01	C3
ATOM 3756 CB ARG 548	60.995	39.213	-0.949	1.00	25.42	C3
ATOM 3757 CG ARG 548	61.820	39.361	0.294	1.00	26.11	C3
ATOM 3758 CD ARG 548	63.280	39.158	-0.054	1.00	24.34	C3
ATOM 3759 NE ARG 548	64.044	39.162	1.189	1.00	32.30	C3
ATOM 3760 IE ARG 548	63.572	38.883	1.995	1.00	0.00	C3
ATOM 3761 CZ ARG 548	65.344	39.518	1.325	1.00	32.66	C3
ATOM 3762 NH1 ARG 548	66.159	39.923	0.335	1.00	34.98	C3
ATOM 3763 NH11 ARG 548	67.107	40.170	0.533	1.00	0.00	C3
ATOM 3764 NH12 ARG 548	65.812	39.981	-0.608	1.00	0.00	C3
ATOM 3765 NH2 ARG 548	65.837	39.518	2.549	1.00	32.03	C3
ATOM 3766 NH21 ARG 548	66.708	39.783	2.708	1.00	0.00	C3
ATOM 3767 NH22 ARG 548	65.250	39.275	3.321	1.00	0.00	C3
ATOM 3768 C ARG 548	58.713	38.997	-1.832	1.00	29.81	C3
ATOM 3769 O ARG 548	57.778	39.790	-1.968	1.00	33.63	C3
ATOM 3770 N ALA 549	58.979	38.102	-2.761	1.00	27.87	C3
ATOM 3771 H ALA 549	59.684	37.436	-2.601	1.00	0.00	C3
ATOM 3772 CA ALA 549	58.227	38.045	-3.984	1.00	27.18	C3

FIGURE 5

ATOM 3773 CB ALA 549	58.797	36.934	-4.857	1.00	28.72	C3
ATOM 3774 C ALA 549	56.748	37.810	-3.770	1.00	25.91	C3
ATOM 3775 O ALA 549	55.896	38.337	-4.468	1.00	26.03	C3
ATOM 3776 N GLY 550	56.421	37.074	-2.748	1.00	26.53	C3
ATOM 3777 H GLY 550	57.103	36.657	-2.185	1.00	0.00	C3
ATOM 3778 CA GLY 550	55.055	36.805	-2.457	1.00	26.08	C3
ATOM 3779 C GLY 550	54.410	38.098	-2.075	1.00	26.94	C3
ATOM 3780 O GLY 550	53.339	38.380	-2.608	1.00	26.39	C3
ATOM 3781 N GLY 551	55.073	38.917	-1.234	1.00	27.78	C3
ATOM 3782 H GLY 551	55.958	38.642	-0.925	1.00	0.00	C3
ATOM 3783 CA GLY 551	54.540	40.212	-0.779	1.00	26.51	C3
ATOM 3784 C GLY 551	54.302	41.113	-1.994	1.00	26.82	C3
ATOM 3785 O GLY 551	53.313	41.852	-2.065	1.00	27.42	C3
ATOM 3786 N VAL 552	53.154	41.013	-3.012	1.00	25.81	C3
ATOM 3787 H VAL 552	53.916	40.396	-2.954	1.00	0.00	C3
ATOM 3788 CA VAL 552	54.952	41.843	-4.176	1.00	28.39	C3
ATOM 3789 C VAL 552	55.917	42.391	-5.150	1.00	26.20	C3
ATOM 3790 CG1 VAL 552	57.327	42.546	-4.594	1.00	26.44	C3
ATOM 3792 C VAL 552	53.650	41.406	-4.020	1.00	29.05	C3
ATOM 3793 O VAL 552	52.744	42.251	-4.888	1.00	31.68	C3
ATOM 3794 N LEU 553	53.455	40.120	-5.176	1.00	27.20	C3
ATOM 3795 H LEU 553	54.122	39.447	-4.908	1.00	0.00	C3
ATOM 3796 CA LEU 553	52.266	39.705	-5.915	1.00	23.80	C3
ATOM 3797 C LEU 553	52.357	38.262	-6.363	1.00	24.86	C3
ATOM 3798 CG LEU 553	53.432	37.955	-7.357	1.00	23.06	C3
ATOM 3799 CD1 LEU 553	54.073	36.623	-7.092	1.00	24.11	C3
ATOM 3800 CD2 LEU 553	52.794	38.061	-8.703	1.00	31.87	C3
ATOM 3801 C LEU 553	51.012	39.825	-5.114	1.00	23.72	C3
ATOM 3802 O LEU 553	49.982	40.138	-5.712	1.00	24.63	C3
ATOM 3803 N VAL 554	50.962	39.580	-3.803	1.00	24.37	C3
ATOM 3804 H VAL 554	51.774	39.350	-3.295	1.00	0.00	C3
ATOM 3805 CA VAL 554	49.660	39.691	-3.180	1.00	26.36	C3
ATOM 3806 C VAL 554	49.472	38.751	-1.802	1.00	26.55	C3
ATOM 3807 CG1 VAL 554	50.696	37.933	-1.418	1.00	23.95	C3
ATOM 3808 CG2 VAL 554	48.953	39.614	-0.682	1.00	25.58	C3
ATOM 3809 C VAL 554	49.322	41.175	-2.960	1.00	27.53	C3
ATOM 3810 O VAL 554	48.142	41.502	-3.192	1.00	27.44	C3
ATOM 3811 N ALA 555	50.277	42.106	-2.716	1.00	28.04	C3
ATOM 3812 H ALA 555	51.221	41.831	-2.658	1.00	0.00	C3
ATOM 3813 CA ALA 555	49.956	43.539	-2.509	1.00	28.57	C3
ATOM 3814 C ALA 555	51.161	44.427	-2.217	1.00	28.07	C3
ATOM 3815 O ALA 555	49.402	44.055	-3.803	1.00	30.12	C3
ATOM 3816 N SER 556	48.425	43.521	-4.839	1.00	26.44	C3
ATOM 3817 H SER 556	49.985	43.521	-4.710	1.00	0.00	C3
ATOM 3818 N SER 556	50.781	42.956	-4.710	1.00	30.09	C3
ATOM 3819 CA SER 556	49.548	43.810	-6.152	1.00	31.42	C3
ATOM 3820 C SER 556	50.684	43.277	-6.965	1.00	37.88	C3
ATOM 3821 OG SER 556	50.442	43.338	-8.344	1.00	0.00	C3
ATOM 3822 H SER 556	49.966	44.144	-8.576	1.00	0.00	C3
ATOM 3823 C SER 556	48.143	43.243	-6.454	1.00	32.78	C3
ATOM 3824 O SER 556	47.287	43.961	-7.003	1.00	34.56	C3
ATOM 3825 N HIS 557	47.750	42.019	-6.088	1.00	32.78	C3
ATOM 3826 H HIS 557	48.350	41.453	-5.560	1.00	0.00	C3
ATOM 3827 CA HIS 557	46.396	41.605	-6.401	1.00	33.64	C3
ATOM 3828 CB HIS 557	46.203	40.142	-6.242	1.00	37.88	C3
ATOM 3829 CG HIS 557	46.986	39.518	-7.348	1.00	42.44	C3
ATOM 3830 CD1 HIS 557	46.694	39.665	-8.675	1.00	43.63	C3
ATOM 3831 ND1 HIS 557	48.104	38.837	-7.209	1.00	45.23	C3
ATOM 3832 HD1 HIS 557	48.641	38.764	-6.385	1.00	0.00	C3
ATOM 3833 CE1 HIS 557	48.524	38.569	-8.414	1.00	46.56	C3
ATOM 3834 HE2 HIS 557	47.676	39.066	-9.283	1.00	45.62	C3
ATOM 3835 HE2 HIS 557	47.793	39.018	-10.257	1.00	0.00	C3
ATOM 3836 C HIS 557	45.383	42.249	-5.520	1.00	32.94	C3
ATOM 3837 O HIS 557	44.256	42.444	-5.934	1.00	33.08	C3
ATOM 3838 N LEU 558	45.744	42.534	-4.280	1.00	33.05	C3
ATOM 3839 H LEU 558	46.657	42.356	-3.986	1.00	0.00	C3
ATOM 3840 CA LEU 558	44.817	43.125	-3.348	1.00	31.91	C3
ATOM 3841 CB LEU 558	45.420	43.107	-1.965	1.00	29.25	C3
ATOM 3842 CG LEU 558	44.605	43.615	-0.818	1.00	26.02	C3
ATOM 3843 CD1 LEU 558	43.279	42.883	-0.742	1.00	25.00	C3
ATOM 3844 CD2 LEU 558	45.496	43.571	0.408	1.00	22.86	C3
ATOM 3845 C LEU 558	44.527	44.521	-3.783	1.00	32.47	C3
ATOM 3846 O LEU 558	43.402	44.544	-3.596	1.00	33.97	C3
ATOM 3847 N GLN 559	45.482	45.231	-4.370	1.00	34.36	C3
ATOM 3848 H GLN 559	46.386	44.855	-4.406	1.00	0.00	C3
ATOM 3849 CA GLN 559	45.255	46.569	-4.912	1.00	36.75	C3
ATOM 3850 CB GLN 559	46.598	47.067	-5.470	1.00	39.63	C3
ATOM 3851 CG GLN 559	46.707	48.543	-5.875	1.00	42.07	C3
ATOM 3852 CD1 GLN 559	46.530	49.618	-4.793	1.00	41.53	C3
ATOM 3853 CD1 GLN 559	45.961	50.687	-5.057	1.00	41.25	C3
ATOM 3854 HE2 GLN 559	46.951	49.416	-3.561	1.00	32.96	C3
ATOM 3855 HE2 GLN 559	47.271	48.328	-3.311	1.00	0.00	C3
ATOM 3856 HE2 GLN 559	47.001	50.190	-2.967	1.00	0.00	C3
ATOM 3857 C GLN 559	44.142	46.635	-5.976	1.00	35.22	C3
ATOM 3858 O GLN 559	43.165	47.404	-5.839	1.00	34.99	C3
ATOM 3859 N SER 560	44.260	45.817	-7.025	1.00	33.46	C3
ATOM 3860 H SER 560	45.083	45.292	-7.154	1.00	0.00	C3
ATOM 3861 CA SER 560	43.222	45.683	-8.049	1.00	32.88	C3
ATOM 3862 CB SER 560	43.693	44.776	-8.088	1.00	34.05	C3
ATOM 3863 CG SER 560	45.021	45.174	-9.281	1.00	42.40	C3
ATOM 3864 CG SER 560	45.042	45.996	-9.783	1.00	0.00	C3
ATOM 3865 C SER 560	41.885	45.133	-7.559	1.00	32.01	C3
ATOM 3866 O SER 560	40.791	45.582	-7.920	1.00	32.23	C3
ATOM 3867 N PHE 561	41.969	44.123	-6.710	1.00	29.50	C3
ATOM 3868 H PHE 561	42.850	43.767	-6.964	1.00	0.00	C3
ATOM 3869 CA PHE 561	40.803	43.529	-6.118	1.00	28.17	C3
ATOM 3870 CB PHE 561	41.237	42.541	-5.040	1.00	26.27	C3
ATOM 3871 CG PHE 561	40.069	41.966	-4.268	1.00	25.68	C3
ATOM 3872 CD1 PHE 561	39.282	40.999	-4.846	1.00	25.44	C3
ATOM 3873 CD2 PHE 561	39.761	42.482	-3.051	1.00	25.45	C3
ATOM 3874 CE1 PHE 561	38.166	40.551	-4.215	1.00	21.49	C3

FIGURE 5

ATOM 3875	CEI	PIE	561	38.635	-2.027	-2.421	1.00	26.89	C3
ATOM 3876	CZ	PIE	561	37.853	41.074	-3.008	1.00	24.79	C3
ATOM 3877	C	PIE	561	39.987	44.645	-5.505	1.00	28.81	C3
ATOM 3878	O	PIE	561	38.789	44.697	-5.731	1.00	29.31	C3
ATOM 3879	N	LEU	562	40.672	45.565	-4.797	1.00	28.39	C3
ATOM 3880	H	LEU	562	41.643	45.462	-4.707	1.00	0.00	C3
ATOM 3881	CA	LEU	562	40.033	46.617	-4.057	1.00	26.51	C3
ATOM 3882	CG	LEU	562	40.964	47.203	-3.074	1.00	23.80	C3
ATOM 3883	CG	LEU	562	41.047	46.411	-1.816	1.00	24.85	C3
ATOM 3884	CDI	LEU	562	42.207	46.868	-1.049	1.00	24.07	C3
ATOM 3885	CDI	LEU	562	39.794	46.551	-1.008	1.00	25.13	C3
ATOM 3886	C	LEU	562	39.586	47.669	-4.988	1.00	29.27	C3
ATOM 3887	O	LEU	562	38.580	48.304	-4.681	1.00	29.83	C3
ATOM 3888	N	GLU	563	40.239	47.871	-6.115	1.00	30.88	C3
ATOM 3889	H	GLU	563	41.052	47.368	-6.325	1.00	0.00	C3
ATOM 3890	CA	GLU	563	39.738	48.908	-6.966	1.00	36.88	C3
ATOM 3891	CB	GLU	563	40.660	49.142	-8.137	1.00	40.80	C3
ATOM 3892	CG	GLU	563	41.999	49.628	-7.682	1.00	48.55	C3
ATOM 3893	CD	GLU	563	43.148	49.277	-8.619	1.00	55.42	C3
ATOM 3894	OEI	GLU	563	44.301	49.283	-8.135	1.00	57.39	C3
ATOM 3895	OEI	GLU	563	42.886	48.986	-9.808	1.00	56.44	C3
ATOM 3896	C	GLU	563	38.375	48.469	-7.466	1.00	39.02	C3
ATOM 3897	O	GLU	563	37.388	49.170	-7.270	1.00	39.09	C3
ATOM 3898	N	VAL	564	38.289	47.255	-8.030	1.00	42.30	C3
ATOM 3899	H	VAL	564	39.107	46.714	-8.074	1.00	0.00	C3
ATOM 3900	CA	VAL	564	37.052	46.683	-8.558	1.00	41.84	C3
ATOM 3901	CB	VAL	564	37.333	45.255	-9.041	1.00	42.27	C3
ATOM 3902	CG1	VAL	564	36.055	44.538	-9.435	1.00	41.17	C3
ATOM 3903	CG2	VAL	564	38.283	45.348	-10.241	1.00	42.11	C3
ATOM 3904	C	VAL	564	36.030	46.709	-7.442	1.00	41.68	C3
ATOM 3905	O	VAL	564	34.892	47.015	-7.697	1.00	42.34	C3
ATOM 3906	N	SER	565	36.419	46.501	-6.206	1.00	42.75	C3
ATOM 3907	H	SER	565	37.333	46.173	-6.063	1.00	0.00	C3
ATOM 3908	CA	SER	565	35.562	46.602	-5.064	1.00	44.85	C3
ATOM 3909	CB	SER	565	36.344	46.013	-3.894	1.00	46.54	C3
ATOM 3910	CG	SER	565	35.590	45.714	-2.731	1.00	51.75	C3
ATOM 3911	HC	SER	565	35.060	46.481	-2.491	1.00	0.00	C3
ATOM 3912	C	SER	565	31.167	48.083	-4.871	1.00	45.70	C3
ATOM 3913	O	SER	565	34.038	48.287	-4.446	1.00	47.59	C3
ATOM 3914	H	TYR	566	35.965	49.093	-5.146	1.00	0.00	C3
ATOM 3915	CA	TYR	566	35.518	50.474	-5.086	1.00	49.68	C3
ATOM 3916	CB	TYR	566	36.765	51.362	-5.164	1.00	56.17	C3
ATOM 3917	CG	TYR	566	36.715	51.622	-6.007	1.00	64.64	C3
ATOM 3918	CD1	TYR	566	36.715	51.622	-6.007	1.00	69.53	C3
ATOM 3919	CD2	TYR	566	37.264	52.538	-7.278	1.00	69.53	C3
ATOM 3920	CEI	TYR	566	37.212	53.613	-8.151	1.00	73.71	C3
ATOM 3921	CE2	TYR	566	36.109	53.797	-5.569	1.00	67.98	C3
ATOM 3922	CE2	TYR	566	36.048	54.888	-6.441	1.00	72.92	C3
ATOM 3923	CE2	TYR	566	36.599	54.787	-7.735	1.00	75.29	C3
ATOM 3924	CHI	TYR	566	36.538	55.838	-8.652	1.00	77.42	C3
ATOM 3925	HIH	TYR	566	36.905	55.565	-9.404	1.00	0.00	C3
ATOM 3926	CEI	HIS	571	29.595	51.595	-11.439	1.00	86.01	C3
ATOM 3927	CEI	HIS	571	29.595	51.595	-11.439	1.00	86.01	C3
ATOM 3928	O	TYR	566	34.514	50.696	-6.217	1.00	48.48	C3
ATOM 3929	N	ALA	567	33.545	51.376	-5.950	1.00	46.35	C3
ATOM 3930	H	ALA	567	34.679	50.115	-7.417	1.00	49.14	C3
ATOM 3931	CA	ALA	567	35.512	49.625	-7.572	1.00	0.00	C3
ATOM 3932	CB	ALA	567	33.670	50.165	-8.490	1.00	52.09	C3
ATOM 3933	CG	ALA	567	34.210	49.574	-9.788	1.00	48.37	C3
ATOM 3934	CD	ALA	567	32.315	49.449	-8.238	1.00	55.31	C3
ATOM 3935	O	ALA	567	31.226	50.008	-8.501	1.00	56.87	C3
ATOM 3936	N	VAL	568	32.247	48.721	-7.736	1.00	57.66	C3
ATOM 3937	H	VAL	568	33.083	47.729	-7.564	1.00	0.00	C3
ATOM 3938	CA	VAL	568	30.980	47.573	-7.490	1.00	59.61	C3
ATOM 3939	CB	VAL	568	31.119	46.031	-7.330	1.00	58.96	C3
ATOM 3940	CG1	VAL	568	31.239	45.508	-5.911	1.00	60.27	C3
ATOM 3941	CG2	VAL	568	29.851	45.471	-7.922	1.00	60.44	C3
ATOM 3942	O	VAL	568	30.393	48.177	-6.245	1.00	62.66	C3
ATOM 3943	N	LEU	569	29.174	48.154	-6.180	1.00	64.78	C3
ATOM 3944	H	LEU	569	31.075	48.737	-5.248	1.00	66.15	C3
ATOM 3945	CA	LEU	569	32.038	48.719	-5.243	1.00	0.00	C3
ATOM 3946	CB	LEU	569	30.359	49.334	-4.123	1.00	69.85	C3
ATOM 3947	CG	LEU	569	31.285	49.858	-3.023	1.00	69.91	C3
ATOM 3948	CD	LEU	569	32.007	48.887	-2.095	1.00	70.17	C3
ATOM 3949	OEI	LEU	569	32.847	49.687	-1.140	1.00	70.19	C3
ATOM 3950	C	LEU	569	31.039	48.054	-1.286	1.00	70.56	C3
ATOM 3951	O	LEU	569	29.567	50.509	-4.667	1.00	72.69	C3
ATOM 3952	N	ARG	570	28.365	50.553	-4.425	1.00	71.80	C3
ATOM 3953	H	ARG	570	30.180	51.391	-5.479	1.00	75.95	C3
ATOM 3954	CA	ARG	570	31.153	51.299	-5.580	1.00	0.00	C3
ATOM 3955	CB	ARG	570	29.510	52.498	-6.173	1.00	78.78	C3
ATOM 3956	CG	ARG	570	30.399	53.068	-7.308	1.00	80.07	C3
ATOM 3957	CD	ARG	570	29.658	54.222	-7.997	1.00	84.16	C3
ATOM 3958	OEI	ARG	570	29.976	54.744	-9.417	1.00	85.66	C3
ATOM 3959	C	ARG	570	28.892	55.690	-8.737	1.00	85.67	C3
ATOM 3960	N	ARG	570	27.971	55.354	-8.727	1.00	0.00	C3
ATOM 3961	H	ARG	570	29.051	56.991	-10.026	1.00	85.06	C3
ATOM 3962	CA	ARG	570	30.240	57.590	-10.082	1.00	84.43	C3
ATOM 3963	CB	ARG	570	31.069	57.056	-9.908	1.00	0.00	C3
ATOM 3964	CG	ARG	570	30.295	58.561	-10.314	1.00	0.00	C3
ATOM 3965	CD	ARG	570	27.958	57.736	-10.154	1.00	84.57	C3
ATOM 3966	CHI	ARG	570	27.059	57.316	-10.030	1.00	0.00	C3
ATOM 3967	C	ARG	570	28.042	58.708	-10.375	1.00	0.00	C3
ATOM 3968	O	ARG	570	28.201	52.009	-6.812	1.00	79.92	C3
ATOM 3969	H	HIS	571	27.107	52.565	-6.709	1.00	79.61	C3
ATOM 3970	CA	HIS	571	29.214	50.417	-7.440	1.00	81.35	C3
ATOM 3971	CB	HIS	571	27.247	50.306	-8.197	1.00	82.75	C3
ATOM 3972	CG	HIS	571	27.882	49.274	-9.167	1.00	83.42	C3
ATOM 3973	CD	HIS	571	28.633	50.079	-10.280	1.00	85.08	C3
ATOM 3974	OEI	HIS	571	28.921	49.579	-11.532	1.00	85.81	C3
ATOM 3975	NDI	HIS	571	29.074	51.303	-10.268	1.00	86.25	C3
ATOM 3976	NDI	HIS	571	29.080	51.900	-9.489	1.00	0.00	C3
ATOM 3977	CEI	HIS	571	29.595	51.595	-11.439	1.00	86.01	C3

FIGURE 5

ATOM	3977	NE2	HIS	571	29.494	50.518	-12.187	1.00	86.28	C3	ATOM	4028	H1	H2O	622	24.393	32.417	14.215	1.00	0.00	W	
ATOM	3978	HE2	HIS	571	29.801	50.468	-13.119	1.00	0.00	C3	ATOM	4029	H2	H2O	622	24.469	31.428	13.112	1.00	0.00	W	
ATOM	3979	C	HIS	571	26.725	49.759	-7.195	1.00	83.31	C3	ATOM	4030	CH2	H2O	623	20.791	28.583	14.218	1.00	50.17	W	
ATOM	3980	O	HIS	571	25.075	50.194	-7.301	1.00	84.06	C3	ATOM	4031	H1	H2O	623	20.499	28.803	13.325	1.00	0.00	W	
ATOM	3981	N	LEU	572	26.540	48.963	-6.158	1.00	83.11	C3	ATOM	4032	H2	H2O	623	19.939	28.549	14.688	1.00	0.00	W	
ATOM	3982	H	LEU	572	27.474	48.824	-5.915	1.00	0.00	C3	ATOM	4033	CH2	H2O	625	21.680	78.881	2.761	1.00	40.48	W	
ATOM	3983	CA	LEU	572	25.527	48.457	-5.241	1.00	83.71	C3	ATOM	4034	H1	H2O	625	21.938	78.856	3.375	1.00	0.00	W	
ATOM	3984	CG	LEU	572	26.083	47.267	-4.454	1.00	83.57	C3	ATOM	4035	H2	H2O	625	22.266	79.246	1.970	1.00	0.00	W	
ATOM	3985	CG	LEU	572	25.439	45.884	-4.721	1.00	83.79	C3	ATOM	4036	CH2	H2O	626	39.089	36.486	9.730	1.00	23.36	W	
ATOM	3986	CD1	LEU	572	25.783	45.386	-6.127	1.00	84.16	C3	ATOM	4037	H1	H2O	626	39.090	35.724	9.672	1.00	0.00	W	
ATOM	3987	CD2	LEU	572	25.958	44.866	-3.714	1.00	84.08	C3	ATOM	4038	H2	H2O	626	39.627	36.872	8.853	1.00	0.00	W	
ATOM	3988	C	LEU	572	24.997	49.511	-4.261	1.00	84.78	C3	ATOM	4039	CH2	H2O	627	42.035	78.320	5.697	1.00	46.19	W	
ATOM	3989	O	LEU	572	24.265	49.192	-3.295	1.00	84.85	C3	ATOM	4040	H1	H2O	627	42.416	77.450	5.832	1.00	0.00	W	
ATOM	3990	N	ALA	573	25.349	50.796	-4.483	1.00	85.56	C3	ATOM	4041	H2	H2O	627	41.243	78.146	5.181	1.00	0.00	W	
ATOM	3991	H	ALA	573	26.020	50.960	-5.174	1.00	0.00	C3	ATOM	4042	CH2	H2O	631	47.227	31.440	6.299	1.00	34.17	W	
ATOM	3992	CA	ALA	573	24.822	51.925	-3.721	1.00	85.90	C3	ATOM	4043	H1	H2O	631	47.533	32.209	5.809	1.00	0.00	W	
ATOM	3993	CB	ALA	573	25.600	53.207	-3.970	1.00	85.79	C3	ATOM	4044	H2	H2O	631	47.442	30.713	5.714	1.00	0.00	W	
ATOM	3994	C	ALA	573	23.373	52.245	-4.057	1.00	87.21	C3	ATOM	4045	CH2	H2O	636	24.043	65.423	-0.336	1.00	73.38	W	
ATOM	3995	OT1	ALA	573	22.610	52.413	-3.099	1.00	88.33	C3	ATOM	4046	H1	H2O	636	24.179	65.781	-1.278	1.00	0.00	W	
ATOM	3996	OT2	ALA	573	23.022	52.309	-5.248	1.00	88.34	C3	ATOM	4047	H2	H2O	636	23.469	66.096	0.054	1.00	0.00	W	
ATOM	3997	CH2	H2O	603	26.735	24.280	5.161	1.00	27.42	W	ATOM	4048	CH2	H2O	638	38.284	67.955	-11.226	1.00	29.97	W	
ATOM	3998	H1	H2O	603	27.332	24.335	4.407	1.00	0.00	W	ATOM	4049	H1	H2O	638	38.283	67.402	-11.580	1.00	0.00	W	
ATOM	3999	H2	H2O	603	26.288	23.435	4.992	1.00	0.00	W	ATOM	4050	H2	H2O	638	39.568	68.046	-11.998	1.00	0.00	W	
ATOM	4000	CH2	H2O	605	47.880	37.960	12.073	1.00	56.30	W	ATOM	4051	CH2	H2O	639	27.930	66.675	-7.733	1.00	41.40	W	
ATOM	4001	H1	H2O	605	47.789	37.874	13.031	1.00	0.00	W	ATOM	4052	H1	H2O	639	28.192	67.028	-6.876	1.00	0.00	W	
ATOM	4002	H2	H2O	605	46.980	37.858	11.753	1.00	0.00	W	ATOM	4053	H2	H2O	639	26.975	66.791	-7.705	1.00	0.00	W	
ATOM	4003	CH2	H2O	607	40.001	49.224	7.214	1.00	40.04	W	ATOM	4054	CH2	H2O	643	50.619	62.802	0.813	1.00	36.55	W	
ATOM	4004	H1	H2O	607	40.471	48.761	7.909	1.00	0.00	W	ATOM	4055	H1	H2O	643	51.575	62.904	0.824	1.00	0.00	W	
ATOM	4005	H2	H2O	607	40.123	48.642	6.457	1.00	0.00	W	ATOM	4056	H2	H2O	643	50.301	63.665	0.525	1.00	0.00	W	
ATOM	4006	CH2	H2O	610	59.683	42.530	-9.698	1.00	38.90	W	ATOM	4057	CH2	H2O	646	62.414	38.097	3.759	1.00	73.55	W	
ATOM	4007	H1	H2O	610	60.312	41.833	-9.477	1.00	0.00	W	ATOM	4058	H1	H2O	646	62.444	38.247	4.461	1.00	0.00	W	
ATOM	4008	H2	H2O	610	59.189	42.046	-10.160	1.00	0.00	W	ATOM	4059	H2	H2O	646	62.287	38.480	-9.555	1.00	65.67	W	
ATOM	4009	CH2	H2O	611	57.176	35.940	-14.220	1.00	34.63	W	ATOM	4060	CH2	H2O	650	28.846	68.630	-10.148	1.00	0.00	W	
ATOM	4010	H1	H2O	611	57.174	36.545	-14.974	1.00	0.00	W	ATOM	4061	H1	H2O	650	29.180	67.844	-8.936	1.00	0.00	W	
ATOM	4011	H2	H2O	611	57.989	36.211	-13.757	1.00	0.00	W	ATOM	4062	H2	H2O	650	51.408	56.331	4.056	1.00	62.40	W	
ATOM	4012	CH2	H2O	612	25.793	27.337	19.130	1.00	29.21	W	ATOM	4063	CH2	H2O	652	50.718	56.333	3.365	1.00	0.00	W	
ATOM	4013	H1	H2O	612	26.709	27.661	19.145	1.00	0.00	W	ATOM	4064	H1	H2O	652	51.052	55.671	4.648	1.00	0.00	W	
ATOM	4014	H2	H2O	612	25.762	26.792	19.929	1.00	0.00	W	ATOM	4065	H2	H2O	652	49.404	56.022	2.161	1.00	51.28	W	
ATOM	4015	CH2	H2O	615	29.766	34.284	9.444	1.00	45.03	W	ATOM	4066	CH2	H2O	653	49.442	55.351	1.474	1.00	0.00	W	
ATOM	4016	H1	H2O	615	30.017	34.618	10.308	1.00	0.00	W	ATOM	4067	H1	H2O	653	49.323	56.829	1.630	1.00	0.00	W	
ATOM	4017	H2	H2O	615	29.113	33.592	9.660	1.00	0.00	W	ATOM	4068	H2	H2O	653	68.215	42.794	-2.563	1.00	40.77	W	
ATOM	4018	CH2	H2O	617	37.316	40.012	10.872	1.00	35.21	W	ATOM	4069	CH2	H2O	654	68.347	41.745	-1.777	1.00	0.00	W	
ATOM	4019	H1	H2O	617	36.600	40.017	11.519	1.00	0.00	W	ATOM	4070	H1	H2O	654	68.189	43.181	-2.190	1.00	0.00	W	
ATOM	4020	H2	H2O	617	37.944	39.376	11.259	1.00	0.00	W	ATOM	4071	H2	H2O	654	66.374	40.425	-2.489	1.00	42.31	W	
ATOM	4021	CH2	H2O	619	40.370	52.041	-7.387	1.00	29.62	W	ATOM	4072	CH2	H2O	655	66.936	41.162	-2.766	1.00	0.00	W	
ATOM	4022	H1	H2O	619	40.672	52.274	-6.779	1.00	0.00	W	ATOM	4073	H1	H2O	655	66.452	39.841	-3.252	1.00	0.00	W	
ATOM	4023	H2	H2O	619	39.505	51.810	-7.052	1.00	0.00	W	ATOM	4074	H2	H2O	655	66.927	41.428	-3.011	1.00	44.08	W	
ATOM	4024	CH2	H2O	621	27.903	32.440	10.664	1.00	39.99	W	ATOM	4075	CH2	H2O	656	66.207	42.071	-4.989	1.00	0.00	W	
ATOM	4025	H1	H2O	621	27.553	33.207	11.141	1.00	0.00	W	ATOM	4076	H1	H2O	656	67.542	41.824	-4.374	1.00	0.00	W	
ATOM	4026	H2	H2O	621	27.929	31.808	11.398	1.00	0.00	W	ATOM	4077	H2	H2O	656	40.371	57.111	5.730	1.00	66.55	W	
ATOM	4027	CH2	H2O	622	25.057	31.972	13.675	1.00	32.70	W	ATOM	4078	CH2	H2O	657							

FIGURE 5

ATOM	4079	H1	H2O	657	39.958	5.259	5.613	1.00	0.00	W
ATOM	4080	H2	H2O	657	40.021	57.651	5.014	1.00	0.00	W
ATOM	4081	OH2	H2O	658	48.780	47.580	-3.122	1.00	52.09	W
ATOM	4082	H1	H2O	658	48.811	46.671	-3.438	1.00	0.00	W
ATOM	4083	H2	H2O	658	49.568	47.955	-3.542	1.00	0.00	W
ATOM	4084	OH2	H2O	663	29.095	62.889	1.825	1.00	39.23	W
ATOM	4085	H1	H2O	663	29.380	62.827	2.739	1.00	0.00	W
ATOM	4086	H2	H2O	663	28.377	63.526	1.887	1.00	0.00	W
ATOM	4087	OH2	H2O	664	27.132	25.640	7.430	1.00	50.65	W
ATOM	4088	H1	H2O	664	26.870	24.838	7.876	1.00	0.00	W
ATOM	4089	H2	H2O	664	27.001	25.362	6.496	1.00	0.00	W
ATOM	4090	OH2	H2O	665	23.367	30.554	12.167	1.00	49.69	W
ATOM	4091	H1	H2O	665	24.026	30.006	11.707	1.00	0.00	W
ATOM	4092	H2	H2O	665	22.941	31.016	11.438	1.00	0.00	W
ATOM	4093	OH2	H2O	666	46.015	32.192	10.179	1.00	66.86	W
ATOM	4094	H1	H2O	666	46.060	31.519	9.497	1.00	0.00	W
ATOM	4095	H2	H2O	666	45.411	31.827	10.833	1.00	0.00	W
ATOM	4096	OH2	H2O	667	38.943	37.883	11.978	1.00	47.87	W
ATOM	4097	H1	H2O	667	39.367	37.487	11.188	1.00	0.00	W
ATOM	4098	H2	H2O	667	38.521	37.114	12.362	1.00	0.00	W
ATOM	4099	OH2	H2O	671	33.437	58.101	2.269	1.00	46.65	W
ATOM	4100	H1	H2O	671	33.555	57.162	2.433	1.00	0.00	W
ATOM	4101	H2	H2O	671	33.962	58.514	2.961	1.00	0.00	W
ATOM	4102	OH2	H2O	672	27.551	31.314	20.022	1.00	30.15	W
ATOM	4103	H1	H2O	672	27.929	32.042	20.533	1.00	0.00	W
ATOM	4104	H2	H2O	672	26.845	31.764	19.552	1.00	0.00	W
ATOM	4105	OH2	H2O	673	25.714	36.908	21.385	1.00	36.95	W
ATOM	4106	H1	H2O	673	24.806	37.123	21.637	1.00	0.00	W
ATOM	4107	H2	H2O	673	25.599	36.284	20.654	1.00	0.00	W
ATOM	4108	OH2	H2O	674	38.244	66.897	12.076	1.00	57.36	W
ATOM	4109	H1	H2O	674	37.773	67.536	12.626	1.00	0.00	W
ATOM	4110	H2	H2O	674	38.153	66.104	12.618	1.00	0.00	W
ATOM	4111	OH2	H2O	675	35.762	36.553	-3.986	1.00	58.40	W
ATOM	4112	H1	H2O	675	35.600	37.449	-3.677	1.00	0.00	W
ATOM	4113	H2	H2O	675	35.549	36.642	-4.923	1.00	0.00	W
ATOM	4114	OH2	H2O	676	30.689	32.814	25.675	1.00	59.30	W
ATOM	4115	H1	H2O	676	30.093	33.571	25.680	1.00	0.00	W
ATOM	4116	H2	H2O	676	31.550	33.214	25.540	1.00	0.00	W

END

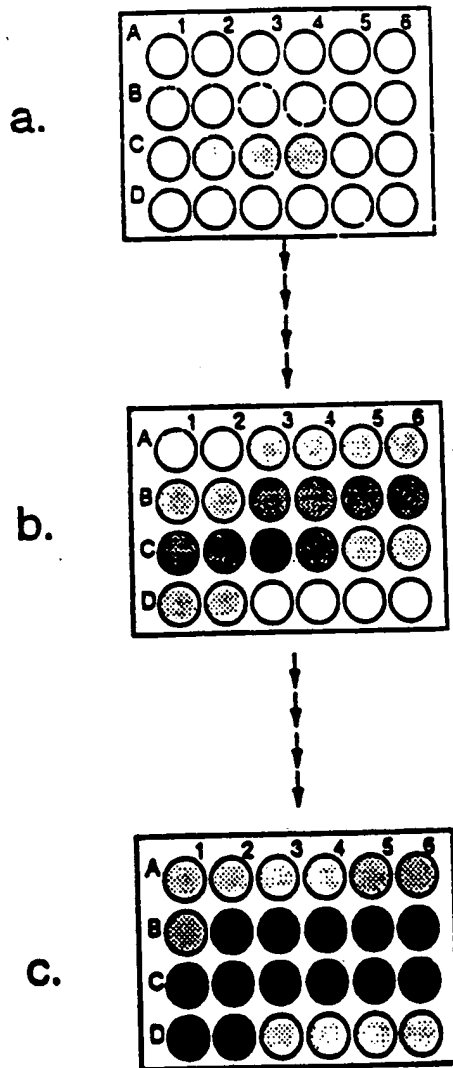


FIGURE 6